Partial dopamine agonists in schizophrenia

Mike Launer

The emergence of partial dopamine agonists reinforces the argument for the dopamine hypothesis of schizophrenia. Aripiprazole (Abilify®) is the first of these compounds for the treatment of schizophrenia to be launched in the UK. Aripiprazole has a promising efficacy and favourable tolerability profile that suggests it has a significant role to play in the management of schizophrenia.

Schizophrenia is a severe psychotic disorder that affects around 1% of the population. The positive symptoms, such as hallucinations and delusions, respond to the older typical antipsychotic drugs (haloperidol, chlorpromazine or the depot injections). However, these older drugs did little for the negative symptoms of schizophrenia (withdrawal, poor motivation and drive). The typical antipsychotics have a high level of dopamine system blockade, causing the extra-pyramidal symptoms (EPS) of Parkinsonism, akathisia and, ultimately, tardive dyskinesia. In many cases, these symptoms were more disabling than the symptoms of the disorder itself, and caused secondary negative symptoms such as depression and suicidal feelings.

The re-introduction in 1990 of clozapine, heralded a new approach and was an important advance in the pharmacotherapy of schizophrenia. This drug, plus its successors, especially risperidone, quetiapine and olanzapine, produced less dopamine blockade, especially in the nigrostriatal system of the brain, and so were associated with substantially lower liability for EPS and a reduced risk of tardive dyskinesia compared with first-generation agents, such as the phenothiazine group.

This issue was highlighted by recommendations from the National Institute for Clinical Excellence (NICE) in 2002, who advised that atypical antipsychotics should be used as first-line treatment for those with newly diagnosed schizophrenia. After a thorough review of the data, NICE found that atypical antipsychotics had definite benefits over typical antipsychotics, particularly in regard to their likelihood of causing EPS. The improved tolerability profile of atypical antipsychotics has been attributed to their serotonin 5HT2A receptor antagonism and/or 5HT1A partial agonism, in addition to their reduced dopamine D2 receptor antagonism (Meltzer, 1999). However, NICE guidance recognized that the 'newer' drugs were still associated with a range of side-effects, such as weight gain, metabolic problems and raised prolactin levels (causing sexual and bone density reduction).

The atypical antipsychotic sertindole caused cardiac rhythm abnormalities and has now been withdrawn in the UK. Blood dyscrasias had long been recognized as a problem with clozapine treatment, and mandatory blood monitoring has largely controlled this problem. Remoxipride's propensity to cause aplastic anaemia caused its withdrawal in the early 1990s.

Although the introduction of atypical antipsychotics had brought some relief to the quality-of-life issues associated with typical antipsychotics, their adverse effects are associated with long-term health risks, as well as compliance issues.

PARTIAL DOPAMINE AGONISTS

The dopamine hypothesis for schizophrenia postulates that hyperactivity of dopaminergic transmission at the D2 receptor is responsible for psychotic symptoms (*Figure 1*).

This hypothesis originates from studies conducted by Professor Arvid Carlsson, professor of pharmacology at Gothenburg University in Sweden, and his colleagues in 1963. Professor Carlsson received the 2000 Nobel Prize in Medicine for his discovery in the late 1950s that dopamine is a neurotransmitter in the mammalian brain and has a critical role in psychiatric illnesses.

Professor Carlsson et al believed that dopamine stabilizers would offer significant advantages over existing drugs because the pathophysiological mechanism of schizophrenia is thought to be based on too much dopamine activity in some areas of the brain and too little in others.

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It is now widely accepted that, while positive symptoms are caused by dopaminergic hyperactivity and D2 hyperstimulation in the mesolimbic pathway, negative symptoms are possibly caused by dopaminergic hypoactivity and suboptimal stimulation of the D1 receptor in the mesocortical pathway (Stahl, 2002). Absolute D2 antagonism offers little efficacy against negative symptoms. In the dorsal nigrostriatal and tuberoinfundibular pathways, absolute D2 antagonism is associated with EPS and elevates prolactin, respectively. Absolute D2 antagonism in the mesolimbic system and ventral striatum is therapeutic for positive symptoms, but it can also interfere with the role of dopamine in the reward system and aggravate dysphoria and anhedonia.

What was needed was a new generation of antipsychotics that could stabilize the dopaminergic and serotonergic pathways through a combination of partial agonism at both dopamine D2 receptors and serotonin 5HT1A receptors, and antagonism at 5HT2A receptors, offering benefits for both positive and negative symptoms without the EPS, hyperprolactinaemia and dysphoria associated with absolute dopamine antagonism.

PARTIAL AGONISTS

Partial agonists work like a thermostat on the D2 system. They act as an antagonist in areas of high levels of dopamine, but not where there are normal levels of dopamine. Moreover, where there are low levels of dopamine, a partial agonist shows functional agonist activity. The overall effect is to stabilize dopamine activity. Aripiprazole (Abilify) has potent affinity as well as moderate partial agonist activity at D2 receptors, and is the first of dopamine system stabilizer for the treatment of schizophrenia to be launched in the UK.

CLINICAL TRIALS

The efficacy of aripiprazole in acute psychosis has been demonstrated in a number of short-term clinical trials. Data from five 4–6-week, double-blind, multicentre studies of patients hospitalized with acute relapse of schizophrenia or schizoaffective disorder randomized to aripiprazole (n=932), placebo or haloperidol (n=201) (Marder et al, 2003), has been pooled and analysed. The daily dose of aripiprazole ranged from 2 to 30 mg. This analysis concluded that aripiprazole at a dose of 15 or 30 mg/day was associated with statistically significantly greater improvements in psychotic symptoms compared with placebo. There were no significant differences between aripiprazole and placebo on Simpson-Angus Scale scores (SAS), no dose-dependent effects on Barnes akathisia scores (BAS) and significant reductions

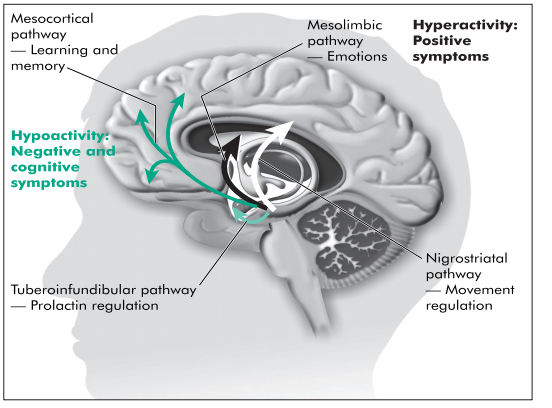


Figure 1. Dopamine hypothesis of schizophrenia

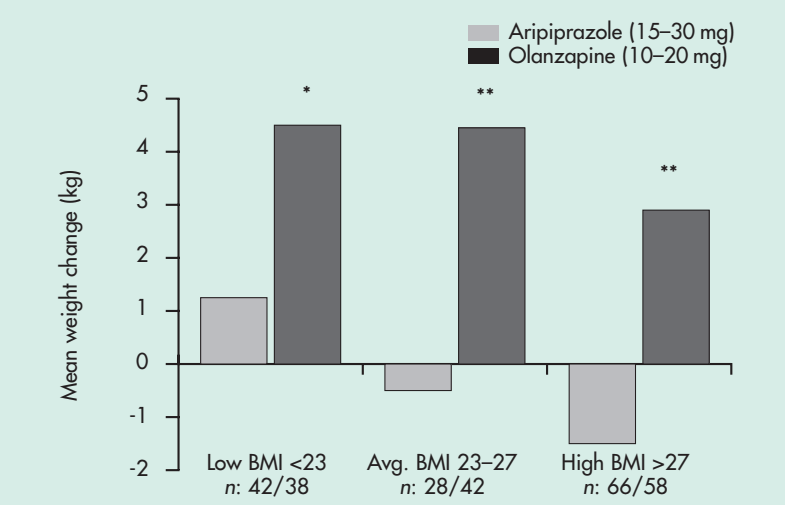
in abnormal involuntary movement scale (AIMS) scores from baseline *vs* placebo ($P \leq 0.01$). The analysis also found that aripiprazole was well tolerated, with similar adverse event incidence rates to placebo and lower rates than haloperidol for akathisia, EPS and somnolence. There was minimal mean weight change with aripiprazole and a lack of QTc (interval determined by fractional exponent correction method) prolongation.

The efficacy of aripiprazole has also been demonstrated in long-term clinical trials. In a trial of 1294 patients diagnosed with acute relapse of schizophrenia and given either aripiprazole 30 mg daily or haloperidol 10 mg daily, significantly more patients responded and remained on treatment with aripiprazole than with haloperidol – 40% *vs* 27% ($P < 0.001$) (Kasper et al, 2003).

The positive and negative syndrome scale (PANSS) total score had fallen by 20.7 in the haloperidol group and by 22.2 among those taking aripiprazole (P = not significant) at 26 weeks. PANSS negative subscale scores had fallen by 4.4 for those on haloperidol and 5.1 for those on aripiprazole ($P < 0.05$). Montgomery-Asberg depression rating scale total score fell by 2.0 for those taking haloperidol and 2.9 for those on aripiprazole ($P < 0.05$).

In a separate 26-week study of 310 patients with stable chronic schizophrenia, aripiprazole was associated with fewer relapses than placebo (57% *vs* 34%). The time to relapse was also significantly longer for aripiprazole compared with placebo ($P < 0.001$) (Pigott et al, 2003). The incidence of adverse events was similar in both treatment groups, with most being mild to moderate.

Data from a 26-week trial of 317 patients with acute relapse of schizophrenia randomized to receive either aripiprazole (15–30 mg/day) or olanzapine (10–20 mg/day) (McQuade et al, 2003), presented at the American Psychiatric Association meeting in May 2003, found that significantly more olanzapine-treated patients experienced clinically significant weight gain (defined as ≤7% increase from baseline weight) than arip-



Observed case analysis in 26 week weight gain trial; significantly greater than aripiprazole,* $P<0.01$, ** $P<0.001$

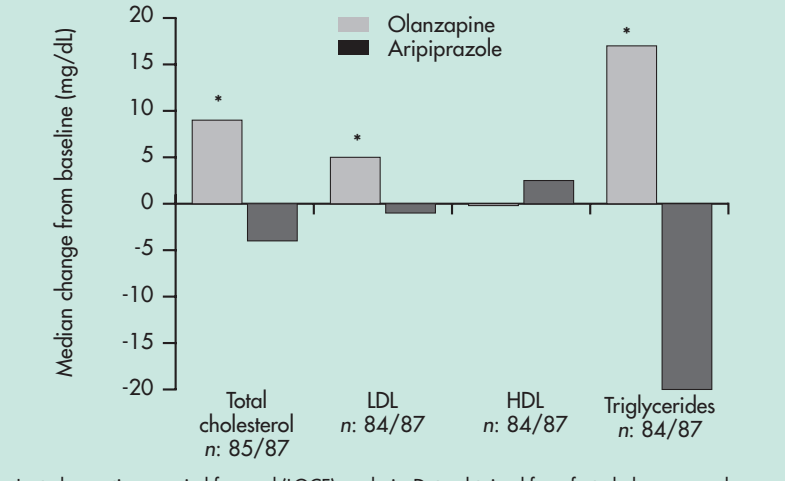
Figure 2. Long term aripiprazole treatment did not induce weight gain. BMI = Body mass index (McQuade et al, 2003).

iprazole-treated patients (37% *vs* 14%; $P<0.001$) (*Figure 2*). Efficacy was comparable between the two drugs. Moreover, a significantly greater percentage of olanzapine-treated patients who started with baseline values experienced elevated total cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides during the course of the study compared with those treated with aripiprazole (*Figure 3*).

The efficacy of aripiprazole treatment in patients with schizophrenia or schizoaffective disorder switched from other agents has also been studied. Casey et al (2003) studied 311 stable patients switched to aripiprazole from a number of other antipsychotics (olanzapine, risperidone or haloperidol). Efficacy was maintained with aripiprazole during the study with numerical improvements in PANSS, and in prolactin, weight, QTc and EPS scales in all three groups. In this 8-week study, the effects were seen irrespective of which initial treatment had been prescribed and across all switching strategies used – switching to aripiprazole 30 mg daily without titration (immediate start), switching to aripiprazole 30 mg daily tapering off before treatment (taper prior), and switching to aripiprazole with titration to 30 mg daily while simultaneously tapering previous treatment (taper both). Patients in the immediate start group experienced a 7.59 fall in total PANSS score, the taper prior group an 8.18 reduction, and the taper both group a 10.11 reduction.

In all groups there was an improvement in EPS. Some groups also showed a modest improvement in dyskinesia. The majority of adverse events reported were mild to moderate – the most common was insomnia.

Figure 3. Comparison of olanzapine and aripiprazole with regard to their effect on mean plasma lipid levels.



Last observations carried forward (LOCF) analysis. Data obtained from fasted plasma samples; *$P<0.05$: Baseline values – Cholesterol: O=185, A=184; low density lipoprotein: O=110, A=108; high density lipoprotein: O=44, A=44; triglycerides: O=159, A=162 (Pigott et al, 2003)

SAFETY AND TOLERABILITY

In short- and long-term trials (Kasper et al, 2003; Marder et al, 2003), aripiprazole has been shown not to be associated with QTc prolongation (*Figure 4*). As stated before, some of the most troublesome side-effects of drugs used for treating schizophrenia tend to be EPS, weight gain, electrocardiogram changes, sexual dysfunction and sedation.

In the aripiprazole switch study (Casey et al, 2003), patients across all switch strategies demonstrated improvement in EPS as measured by SAS, BAS and AIMS (*Figure 5*). In addition, a reduction in prolactin levels was seen in all groups. The most frequently reported adverse event was insomnia. In the long-term maintenance study, aripiprazole was associated with significantly less EPS compared with haloperidol. The incidence of EPS-related adverse events was 27% in the aripiprazole group *vs* 58% in the haloperidol group. The most commonly reported adverse events with aripiprazole were insomnia, anxiety, nausea and akathisia.

CLINICAL PRACTICE

Aripiprazole is effective in a dose range of 15–30mg/day (Otsuka Pharmaceuticals, 2005). The recommended starting dose is 15mg/day administered on a once-a-day schedule without regard to meals. In clinical practice, most patients require a 15 mg dose of aripiprazole, and it is useful to warn patients about the side-effects of nausea and vomiting, which may be troublesome for the first 2–4weeks. Experience shows that this is best treated with metoclopramide, but taking the dose after a meal or using an antihistaminic (e.g.

cinnarizine) is advised. Insomnia may be treated with zopiclone temporarily. As aripiprazole is a non-sedating drug, some patients may be troubled by anxiety and benzodiazepines can be used. In many cases weight loss may be quite rapid if they have previously used atypical antipsychotics, and this is often a welcome side effect.

CONCLUSIONS

In the 1950s the phenothiazine-type drugs were a breakthrough and their conversion to depot preparations heralded a substantial reduction in the bed numbers for the mentally ill in the UK. The recognition of EPS as a significant factor in the (poor) quality of life in schizophrenia stimulated the emergence of the atypical antipsychotics. Clozapine was the benchmark for the atypicals, and the only drug proven to be effective for treatment-resistant cases.

Although clozapine maintains its position, the other atypicals have introduced new problems. Obesity, diabetes, raised prolactin and cardiac arrythmias are seen as new quality-of-life issues. Partial agonists are the obvious solution to some of the side-effect dilemmas and are emerging in clinical practice as also providing effective results. Partial agonists are also effective at treating the positive, negative and cognitive symptoms of schizophrenia. This fits in with the research prediction around dopamine receptors, and time will tell whether this is the third phase of the development of antipsychotics. **HM**

Conflict of interests: Most psychiatric pharmaceutical companies have provided the author with grants for attending national and international conferences

Casey DE, Carson WH, Saha AR et al (2003) *Psychopharmacology* (Berl.) **166:** 391–9

Kasper S, Lerman MN, McQuade R et al (2003) Efficacy and safety of aripiprazole versus haloperidol for long-term maintenance treatment following acute relapse of schizophrenia. *Int J Neuropsychopharmacol* **6:** 325–37

Marder SR, McQuade RD, Stock E et al (2003) Aripiprazole in the treatment of schizophrenia: safety and tolerability in short-term, placebo-controlled trials. *Schizophr Res* **61:** 123–36

McQuade RD, Jody DN, Kujawa MJ et al (2003) Long-term weight effects of aripiprazole *vs* olanzapine. Poster at American Psychiatric Association Annual Meeting. 17–22 May 2003. San Francisco, California

Meltzer HY (1999) The role of serotonin in antipsychotic drug action. *Neuropsychopharmacology* **21**(2 suppl): 106S–15S

National Institute for Clinical Excellence (2002) *Guidance on the Use of Newer (Atypical) Antipsychotic Drugs for the Treatment of Schizophrenia*. Technology appraisal guidance, No. 43. NICE, London

Otsuka Pharmaceuticals (2005) Abilify. Summary of product characteristics. Otsuka Pharmaceuticals (UK) Ltd, London

Pigott TA, Carson W, Saha A, Torbeyns AF, Stock EG, Ingenito GG (2003) Aripiprazole for the prevention of relapse in stabilised patients with chronic schizophrenia: a placebo-controlled 26-week study. *J Clin Psychiatry* **64:** 1048–56

Stahl SM (2002) *Essential Psychopharmacology of Antipsychotics and Mood Stabilisers*. 1st edn. Cambridge University Press, Cambridge

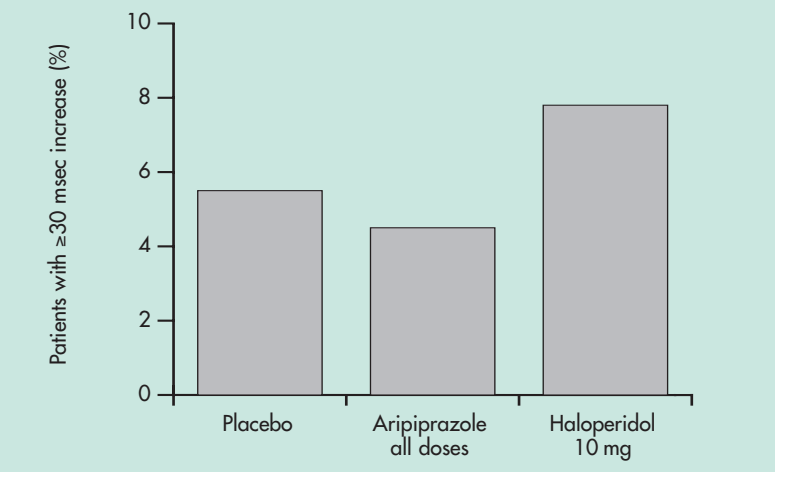
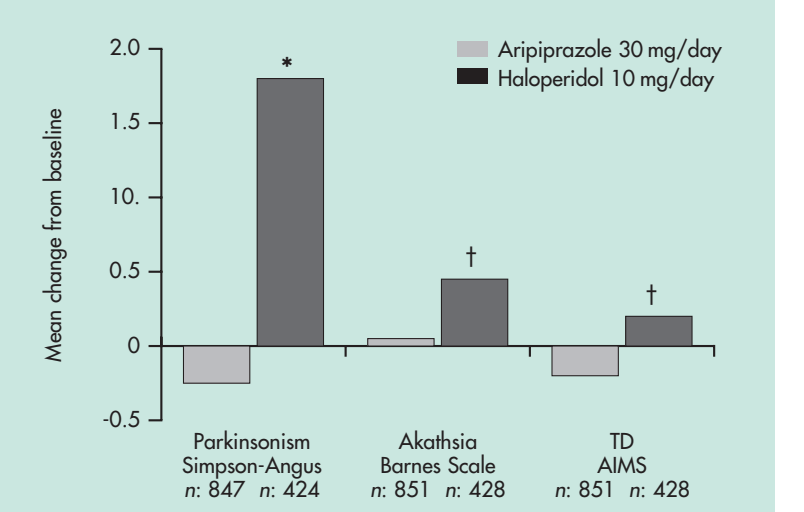


Figure 4. Aripiprazole short-term clinical trials. Effects on QT_c interval. Clinically meaningful QT_c interval (>450 msec occured in two patients treated with aripiprazole. No patient had a QT_c interval of >500 msec. QT_c = interval determined by fractional exponent correction method. (Marder et al, 2003).



*P <0.0001; †P >0.001; last observations carried forward (LOCF) analysis
AIMS = Abnormal Involuntary Movement Scale; TD = Tardive dyskinesia

Figure 5. Extra-pyramidal symptoms during long-term trials. Comparison of aripiprazole with haloperidol at 52 weeks (Kasper et al, 2003).

KEY POINTS

- The treatment of schizophrenia has evolved via typical to atypical antipsychotics and now to dopamine stabilizers.
- The typical drugs were associated with profound extra-pyramidal symptoms and possible untreatable tardive dyskinesia.
- The atypical drugs reduced extra-pyramidal symptoms, but produced blood dyscrasias, obesity, diabetes mellitus, cardiac arrhythmias and prolactin elevation.
- Partial agonists are a logical extension of the dopamine hypothesis of schizophrenia.
- Aripirazole is the first dopamine partial agonist to be effective and well tolerated in clinical trials.
- In practice, patients both chronic and first episode show good tolerability and improvement in both positive and negative symptoms.
- Partial agonists represent a significant step forward in the choice of treatment for schizophrenia.