Clinical use of aripiprazole in patients with schizophrenia: A real-life setting results from the German Postmarketing Surveillance Study

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Abstract
When aripiprazole (ABILIFY®) received its approval in Germany for the treatment of schizophrenia, a hospital-based postmarketing surveillance study was initiated in order to gain further insights concerning safety and efficacy of the antipsychotic under real-life conditions. Efficacy was rated by using standard CGI, GAF, and SF-12 instruments, whereas safety was evaluated according to the reports on adverse effects. Data from 799 patients with schizophrenia from 122 psychiatric hospitals returned for evaluation. Eighty percent of the patients were treated for 4 weeks with 10–30 mg/day aripiprazole (mean modal dose 15 mg/day). Within the observation period significant improvements of CGI, GAF, and SF-12 ratings was observed. Aripiprazole was tolerated well by the patients. Most frequent adverse effects were insomnia, irritability, restlessness, nausea and vomiting, in general being moderate to mild and corresponding to the known tolerability profile of aripiprazole. The results demonstrate that the administration of aripiprazole can result in an improvement of the symptoms of schizophrenia within 4 weeks in a real-life hospital-based in- and outpatient setting.

Key words: Aripiprazole, schizophrenia, product surveillance, efficacy, tolerability

Introduction
Aripiprazole, an antipsychotic used for the treatment of schizophrenia in the USA since 2002, was introduced into market in Germany in June 2004. Aripiprazole is effective in a dose range from 10 to 30 mg, administered once daily. A starting and maintenance dose of 10–15 mg/day is recommended (Bristol-Myers Squibb 2006). Aripiprazole doses exceeding the recommended daily dose of 15 mg have not been proven to improve therapeutic efficacy. However, individual patients may benefit from higher dosages. Aripiprazole can be taken without regard to meals or time of day.

Aripiprazole has a unique mechanism of action, different from all currently available antipsychotic agents. Aripiprazole is a partial agonist at dopamine D2 and serotonin 5-HT1A receptors as well as an antagonist at 5-HT2A receptors (Burris et al. 2002; Jordan et al. 2002; Hirose et al. 2004). In an animal model the substance has been shown to reduce dopaminergic transmission in regions of dopamine overactivity while acting as an agonist in areas with low dopamine transmission (Kikuchi et al. 1995). In vitro, aripiprazole binds with high affinity to dopamine D2 and D3 receptors as well as to serotonin 5-HT1A and 5-HT2A receptors (Jordan et al. 2002; McQuade et al. 2002). It binds with lower affinity to dopamine D4, serotonin 5-HT2C and 5-HT7 receptors, α1-adrenergic and to H1 receptors (McQuade et al. 2002). There is no appreciable binding to muscarinic receptors (McQuade et al. 2002).

The efficacy of aripiprazole with significant improvements of positive and negative symptoms of schizophrenia as well as its safety and tolerability has been proven in several controlled clinical short- and long-term trials (see reviews Lambert et al. 2004; Lieberman et al. 2005; Klein et al. 2006). In order to allow for a homogeneous population of patients, controlled studies rather apply strict criteria for inclusion and exclusion of patients. Thus, patients with multiple diagnoses and concurrent diseases...
and/or medications frequently are excluded from a study. However, to generate further experience close to health care reality, naturalistic studies have to be performed. Accordingly, some aripiprazole premarketing studies were initiated such as the international open, prospective, randomised parallel group BETA (Broad Effectiveness Trial with Aripiprazole) trial. In the USA 1599 patients with schizophrenia or schizoaffective disorder were included in the BETA trial (Tandon et al. 2006), in Europe 833 patients (Beuzen et al. 2006b). Patients were treated with either aripiprazole 10–30 mg/day or other, mainly atypical antipsychotics. By using CGI-I (Clinical Global Impression – Improvement Scale) rating scale and the POMS (Preference of Medication Scale) aripiprazole was demonstrated in the USA as well as in Europe under real-life conditions to effectively reduce symptoms of schizophrenia. Furthermore, aripiprazole was well tolerated by the patients. In the European open STAR (Schizophrenia Trial of Aripiprazole) trial 555 patients with schizophrenia were included who were treated by psychiatric specialists in hospital and practice (Beuzen et al. 2006a; Hanssens et al. 2006). Patients received aripiprazole or other atypical antipsychotics for 26 weeks. Aripiprazole produced improvements in terms of efficacy (Investigator’s Assessment Questionnaire, IAQ, CGI-I, Clinical Global Impression – Severity of Disease Scale, CGI-S), quality of life and tolerability compared to the control group (Beuzen et al. 2006a; Hanssens et al. 2006). Both, in the BETA and the STAR trials aripiprazole proved to be an efficient antipsychotic in clinical practice. It is not only tolerated well but also improves quality of life in outpatients and inpatients with schizophrenia.

Extending previous observational trials, the aim of the present Germany-based postmarketing surveillance study was to study efficacy, tolerability and safety of aripiprazole in patients with schizophrenia who were treated and followed-up in psychiatric hospitals and/or an outpatient clinics, exclusively.

Materials and methods

Subjects

Specialized clinical psychiatrists were asked to refer patients with schizophrenia in whom treatment with aripiprazole was indicated according to their free decision. Patients were suffering from any subtype of schizophrenia according to the International Classification of Diseases (ICD). Patients were either inpatients and/or in the hospital’s outpatient clinic. Due to the random inclusion of the patients driven only by clinical judgement as well as due to the multicentric design of the study, patient population was considered to be representative.

Study design

This surveillance study was a multicentric, prospective cohort study that fulfilled the requirements of the German Drug Law (AMG) sponsored by the manufacturers of aripiprazole (ABILIFY®), Bristol-Myers Squibb and Otsuka Pharmaceutical. The surveillance was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. In each centre, up to 10 in- or outpatients were documented within a period of 4 weeks. Following the first visit there were two further visits after 1 and 2 weeks of treatment and a final visit at week 4. Data were assessed from June to December 2004 by using standardized questionnaires (CRFs). All documents were controlled for completeness and plausibility by a contract research organization.

On the first visit, demographic data and medical history of the patients, psychopharmacological and other medication, additional non-pharmacological treatment measures, concurrent diseases as well as psychosocial status were assessed.

Patients were either treated with aripiprazole for the first time or switched to aripiprazole. A switch was mainly performed when previous antipsychotics were not efficient enough or not tolerated. Participating physicians were asked to specify the starting dose and the time of administration of aripiprazole. On the first interim visit, if applicable, the procedures of tapering the previous antipsychotic medication as well as the status of up-titration of aripiprazole, if applicable, were put on record. On all interim visits, changes of any medication, undesired side effects and body weight were documented. Efficacy parameters were assessed on all evaluation visits.

Efficacy parameters

Efficacy of treatment was assessed by using standardized instruments which can easily be applied in clinical routine without major inconvenience for the patients. Severity of disease, changes of clinical condition and efficacy index (therapeutic efficacy and risks of therapy) were assessed by the participating physician using the Clinical Global Impression (CGI) scale. Psychological, social and vocational functions of a patient were assessed by the Global Assessment of Functioning (GAF) (Endicott et al. 1976; American Psychiatric Association 1994). Higher GAF scores indicate better functioning. GAF scores were classified in five categories: 1–40,
pervasive impairment; 41–50, serious impairment; 51–60, moderate impairment; 61–70, mild impairment; and 71–90, minimal impairment (Jones et al. 1995; Moos et al. 2002). Additionally, the Short Form Health Survey-12 (SF-12), a short form of SF-36, was applied. This questionnaire covers the patients’ physical and mental health state (Ware et al. 1996, 1998) (self-rating). Undesired effects were assessed on each follow-up visit and reported.

Statistical analysis

Descriptive statistical analysis was performed for all data at the end of the study (SYSTAT and SAS). Continuous variables (size, age, periods of time, etc.) and statistical values (n, mean, median, minimum, maximum, standard deviation, SD) were listed. Discrete variables were indicated categorically in terms of frequency distribution and calculated in percent in relation to the whole patient sample.

Plain text answers were transferred to adequate coding schemes and analysed as frequency distributions. Categorical-scaled paired follow-up data were presented as contingency tables (first versus last visit). All reports on side effects were transferred into a line listing and transmitted to the sponsor.

Results

Adherence to observation intervals

In most cases, participating patients and physicians adhered to the planned observation intervals. The mean time period between the first visit and the first ingestion of aripiprazole was 1.2±6.6 days (plan: 1 day), between first to second visit 8.3±5.3 day (plan: 7 days), between second to third visit 8.1±5.2 days (plan: 7 days) and between third visit and final documentation 14.3±6.7 days (plan: 14 days). Mean observation period was 30.1±10.9 days (plan: 28 days).

Demographic data

Data from 779 patients originating from 122 clinical centres were included. Eighty percent of the patients were treated as inpatients and 15% in outpatient clinics. Five percent of the data were missing. The proportion of women versus men was roughly balanced. Mean age was 36.7±12.6 years, the median age of the women being slightly higher than of the men (39.2 vs. 31.7 years). Table I shows the demographic and clinical data of the patients.

Sixty-six percent of the patients were singles, 29% were or had been married, 23% had children. The majority of the patients (84%) lived alone or with their families but without any special support. Up to 43% were estimated to work in a job which corresponded to their age including employed persons (16.9%), persons in job training (10.5%), military or social duties (0.3%), working as housewives, house husbands or caring members of the family (5.8%). Of the patients, 9.1% were over 55 years of age. When including all retired persons, 61% of the patients had an earned income. The proportion of employed persons increased along with the level of professional formation. Only 4% of the patients without job training, but 30% of the patients with university degree were employed. Forty-one percent of the patients had a university degree or an O-level certificate, were not employed and lived alone or in their families. Need of subsidy (assisted or therapeutic living, nursing home) and homelessness were observed almost only in persons who were not employed (1.3%).

Clinical characteristics at baseline

The most frequent subtype of schizophrenia was paranoid schizophrenia (54%). Much less patients had hebephrenic or residual schizophrenia (Table I). Participating physicians rated the severity of disease in 81% of the patients as markedly severe or severe. About two-thirds of the schizophrenic patients suffered from positive or negative as well as from concurrent cognitive symptoms. Forty percent of the patients exhibited both positive and negative symptoms of schizophrenia. Cognitive symptoms were more frequently observed in patients who presented negative symptoms than in patients without negative symptoms (46 vs. 22%). Accordingly,
the occurrence of positive symptoms did not correlate with cognitive deficits.

At the initial visit, 87% of the patients received antipsychotics, 39% hypnotics, 25% antidepressants, 8% phase prophylactics or mood stabilisers, and 16% other unspecified medicines. Most of the patients received more than one psychopharmacologic drug; a mean of 2.2 psychopharmacological drugs were administered in each patient with a maximum of six drugs. Only 9% of the patients did not receive any psychopharmacological drug when included in the surveillance study.

Concerning additional treatments, physicians reported that 65% of the patients were subjected to occupational therapy, 51% to psychoeducation, 40% to sociotherapy, and 35% to other forms of therapy.

Concerning substance use, 46% of the patients consumed nicotine and 10% alcohol. In 18% of the patients, an abuse of drugs and/or medicines was present. In 27% of the patients, physicians reported the presence of non-psychiatric diseases, 25% were administered additional medication.

Characteristics of switching to aripiprazole

Patients with schizophrenia were switched to aripiprazole due to inadequate efficacy in negative (55%) or positive (43%) symptoms or due to poor tolerability (36%) of the previous medication. Most patients were switched from olanzapine (19.08%) or risperidone (14.08%) followed by amisulpride (11.53%) and quetiapine (8.83%). Aripiprazole was mainly taken once a day (96%) in the morning (88%). Mean modal daily dose was 15 mg. With few exceptions, switching was not performed by cautiously up-titrating the dose of aripiprazole. 69% of the patients who did not discontinue the study (see below) received a single starting dose of ≥15 mg. The starting dose was maintained until the end of the study in 40% of these patients and increased in 51%.

Efficacy of aripiprazole

GAF. Global functioning as assessed by the GAF scale improved from 38.4±13.6 to 54.1±15.9 at the end of the observation period. The magnitude of change was significant, averaging −15.8±14.5 points (P<0.0001).

On average, most patients improved for more than one main category within the 4-week treatment period and reached a value above the score which indicates necessity of professional help (50 points) (Jones et al. 1995; Startup et al. 2002). GAF scores were analyzed from 582 patients (75%) at the beginning of the study and from 597 patients at the end of the study (77%).

SF-12. The physical health score of the SF-12 scale improved from 42.9±9.9 to 47.5±9.3 within the observation period (Figure 2). The magnitude of change was significant (5.2±8.8 (P<0.0001)). The mental health score improved from 31.3±10.6 to 41.1±11.2 (Figure 2). The patients improved significantly on an average of 9.6±12.2 (P<0.0001). SF-12 scores were analyzed from 688 patients at the beginning of the study (88%) and from 746 patients (96%) at the end of the study.

CGI. At the beginning of the study, 47% of the patients were rated as being “markedly ill”, corresponding to a median CGI of 6 (Figure 3). After 4 weeks of treatment, the severity of illness significantly decreased to a median of 5 or “moderately ill” (P<0.0001).

Relative to the baseline physicians observed improvements in 82% of the patients after 4 weeks of treatment. Forty-one percent of the physicians considered the disease state of their patients have
“much improved” (Figure 4). Accordingly, physicians decided to continue antipsychotic treatment with aripiprazole in 636 patients (81.5%) and rejected further aripiprazole treatment in 61 patients (8.0%). In 82 patients (10.5%), data on subsequent antipsychotic therapy were missing.

**Safety and tolerability of aripiprazole**

A total of 314 adverse effects were reported in 186 of 779 patients (23.8%), most of them being moderate to mild. In 26 patients, adverse effects were classified as being severe. Adverse drug reactions including cases with a causality relationship “not likely” accounted for 90.4% (n=284) of all adverse effects. A total of 55.7% of adverse effects were classified as not severe adverse drug reactions concurring with the expected and known side effect profile of aripiprazole. Most frequent side effects were insomnia, irritability, restlessness, nausea and vomiting. There was no significant change in body weight within the 4-week observation period when patients were switched to aripiprazole (0.08 ± 4.0 kg, \( P = 0.56 \)). Table II shows adverse effects according to the corresponding system organ classes. Psychiatric disorders were the most frequent organ class. However, 32% of these adverse effects were reported as not related or not likely to be related to aripiprazole. In 60% of the reported psychiatric disorders, a clear causal relationship to aripiprazole administration could not be established (“possible”). Psychotic side effects were mainly reported in severely ill, comorbid patients who were partially resistant or did not respond to treatment.

When indexing efficacy and safety aspects, most frequently the physicians considered treatment with aripiprazole or switch to aripiprazole as moderately efficient without risk (34%), minimally efficient without risk (17%) and very efficient without any risk (12%). In 15% of these – according to the physician’s rating – severely and markedly severe ill patients, treatment with aripiprazole did not result in a change or worsening of the disease.

Similar to with the number of patients in whom no improvement was observed a total of 143 patients (18%) discontinued treatment with aripiprazole during the observation period. Most patients who discontinued aripiprazole were treated with doses below 15 mg/day.

**Discussion**

The results of this German postmarketing surveillance study demonstrate that in a hospital-based in- and outpatient real-life setting the administration of aripiprazole to patients with schizophrenia is efficient and safe. Even in patients who were considerably ill and on premedication with other antipsychotics,
aripiprazole improved the clinical status with a low risk for side effects.

First of all, the surveillance study gives insights into the social situation and medical care of patients with schizophrenia in Germany. Consistent with the literature, women and men were equally distributed in the study, but affected men were younger than women (Sadock and Sadock 2002; Möller et al. 2003). According to other studies in high-income welfare societies such as Sweden and the USA (Melle et al. 2000; West et al. 2005), our patients were often unemployed and socially isolated. Also, the level of education or best-ever-occupation predicted the occupational status in our patients. Higher education was related to a higher probability of being employed (Wieselgren and Lindstrom 1996; Melle et al. 2000; Samele et al. 2001). The patients’ characteristics thus underline that schizophrenic patients experience a vicious circle of a low level of education resulting in unemployment and unemployment worsening psychosocial integration of the patients (Floyd 1984). In terms of schizophrenia management, the treatment of severely ill patients before inclusion in this study was characterized by significant polypharmacy, a pattern previously observed in routine psychiatric practice of schizophrenic patients (West et al. 2005). This finding emphasizes the need for more effective pharmacological options with a low risk of drug interactions. In our patients, additional nonpharmacological therapeutic strategies were used frequently. In agreement with current treatment guidelines (Gaebel and Falkai 2005), multimodal treatment of schizophrenia has thus received much attention, above all in more severely ill patients.

Efficacy and tolerability of aripiprazole

In all three rating instruments used in this study, a significant improvement of scores was observed within the observation period of 4 weeks. Aripiprazole improved the severity of disease (CGI-I), the functioning as well as the physical and mental health of the patients with schizophrenia. Significant improvements were observed in the patients’ self-reports (SF-12) as well as in the clinicians’ ratings (GAF). Particularly, patients improved from an initial GAF score below 50, which indicates a need for treatment (Brähler et al. 2002), to a score exceeding 50. In general, our results agree with those from previous surveillance studies such as the BETA studies in the USA (Tandon et al. 2006) and Europe (Beuzen et al. 2006b) as well as the STAR study (Hanssens et al. 2006). The patients who participated in the German surveillance study, however, were more seriously ill. Since the magnitude of improvement of the disease severity score is comparable to the other trials, our data indicate that in a real life setting patients who are more severely ill also benefit from treatment with aripiprazole. In our study, maximal overall improvement was already seen after the 4-week observation period, in the BETA and STAR studies not until after 8 and 26 weeks, respectively. This discrepancy may, however, be due to different disease severities of the patients involved or to different settings of patient care; e.g., our patients were attended only by clinicians in hospitals and not in private practices. The discrepancy may also result from differences in study design that make comparisons difficult: In our study only changes from baseline to endpoint of aripiprazole treatment were analysed. In contrast, BETA and STAR trials compared different treatment arms and distinct endpoints, with patients receiving either aripiprazole or other antipsychotics.

The results of this study indicate that aripiprazole proves to be an effective treatment of schizophrenia under naturalistic conditions. Although comparability is limited, our results may reveal an efficacy benefit of aripiprazole in real-life treatment with respect to the setting of randomized controlled trials. In a placebo controlled study (Kane et al. 2002), patients were less severe ill (CGI-S, 4.9) and improved to a lesser extent after 4 weeks of treatment with aripiprazole (change of CGI-S, 0.6). Similarly, in a long-term trial over 18 months, treatment with atypical antipsychotics resulted in a maximal reduction of CGI-S score of 0.6 (Lieberman et al. 2005).

Aripiprazole was tolerated well by the patients. Only 23.8% of the patients reported side effects, mainly described as being mild to moderate and within the range to be expected and known when treating patients with aripiprazole. Most adverse effects reported in the organ classes “psychiatric disorders” (restlessness, sleep disorders, insomnia) and “nervous system disorders” (headache, dizziness) were not likely or only possibly caused by aripiprazole.

Psychotic side effects reported may be interpreted as the inherent symptoms of schizophrenia. It has particularly to be taken into account that patients were switched to aripiprazole because of the lack of efficiency of previously administered antipsychotics and that patients often were severely ill, treatment resistant and comorbid. Psychotic symptoms may also result from a rebound effect when switching from antipsychotics with a sedative component to aripiprazole.

The safety and tolerability data of the surveillance study are comparable and in part favourable with respect to a meta-analysis of five short-term double-blind trials, although a different classification of
adverse effects was used (Marder et al. 2003). Main psychiatric side effects in the meta-analysis were headache in 31.7%, agitation in 31%, anxiety in 25.1%, and insomnia in 24.1% of the patients (Marder et al. 2003). The favourable side effect profile of aripiprazole, that includes the lack of a significant increase of body weight, may have contributed to the overall improvement of physical and mental health of the patients.

**Switch to aripiprazole**

Switching to another antipsychotic can theoretically be performed by an abrupt discontinuation of the previous and administration of the new antipsychotic or by tapering the previous and up-titrating the new antipsychotic (Correll 2006). If a substance with high affinity for dopaminergic or histaminergic receptors is discontinued and an adequate blood level of the new antipsychotic has not yet been achieved, exacerbation of psychotic symptoms, agitation, insomnia, dyskinesia or akathisia may result. A possible explanation may be that long-term administration of antipsychotics leads to an up-regulation of D2 receptors (Silvestri et al. 2000). Due to aripiprazole’s half-life of 72 h and the achievement of steady state levels not before 2 weeks, fast switching to aripiprazole may result in an abolition of the blockade of up-regulated D2 receptors and consecutively “dopaminergic” withdrawal symptoms. Therefore, a switching strategy specific for the pharmacological profile and the individual patient should be chosen. In the present surveillance study, virtually no physician chose to taper off the previous medication and overlap with aripiprazole treatment. This strategy complied with the previous recommendations for switching to aripiprazole. Increasing experience with the use of aripiprazole, however, indicates that the switch should rather not be performed fast. It is now recommended to apply an overlapping switch which lasts at least 2 weeks (Travis et al. 2005). Concerning dosing, most psychiatrists chose the starting dose of 15 mg/day as recommended at the time the trial was conducted. In the meantime, the recommended starting dose was changed to 10 or 15 mg/day. (Bristol-Myers Squibb, 2006). Most physicians did not change aripiprazole dosage during treatment up to the end of the observation period. When taking into account efficacy and safety, the majority of the participating clinical psychiatrists evaluated the treatment with aripiprazole as efficient and safe.

Recently, a meta-analysis of 31 trials with 10058 subjects outlined dropout rates of 48.1% in placebo-controlled trials and of 28.3% in trials with active control (Kemmler et al. 2005). Hence, a dropout of 143 patients (18.0%), as observed in the present surveillance study, has to be considered as being relatively low. Most of the schizophrenic patients thus adhered to aripiprazole treatment after switching medication. When taking into account that more than 80% of the participating physicians affirmed to continue aripiprazole administration, both physicians and patients appeared to favour aripiprazole treatment in comparison to treatment with other antipsychotics. The dropout rate in this study may also reflect the limited number of patients who did not benefit from aripiprazole treatment since the same number of patients (including patients with missing data) was classified as unchanged or even worsened by the physicians. Furthermore, it has to be considered that these patients in general only received low doses of 15 mg/day aripiprazole. Response to aripiprazole and dropout rate therefore would have been even more favourable if the switching strategy had been optimized and the dosage adequately increased.

The results of this surveillance study support aripiprazole being an efficient antipsychotic drug. There are some limitations of the study, though. Like in other observational studies, treatment regimens were heterogeneous, the data on treated persons did not include assessment of the reasons for stopping therapy, and there were no predefined endpoints. The study therefore was not capable of scientifically proving or disproving hypotheses such as the efficacy and safety of treatment. Due to the heterogeneity of the real-life setting, observational studies are difficult to analyse and interpret. These studies, however, add important insights on the way patients are treated in the real world. The present study demonstrates that aripiprazole is a reasonable and safe treatment option also for severely ill patients pretreated with other antipsychotics in a psychiatric routine setting.

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**Statement of interest**

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