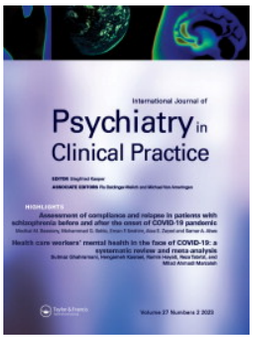

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REVIEW ARTICLE

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Switching antipsychotics to partial dopamine D2-agonists in individuals affected by schizophrenia: a narrative review

Pierre Baumann[a], Philipp Bauknecht[b], Maxim Kuzin[c] and Georgios Schoretsanitis[d,e,f]

[a]Lausanne University Hospital, University of Lausanne, Lausanne, Switzerland; [b]Dr. Carl GmbH, Stuttgart, Germany; [c]Clienia Schloessli, Private Psychiatric Hospital and Academic Teaching Hospital of the University of Zurich, Oetwil am See/Zurich, Switzerland; [d]Department of Psychiatry, The Zucker Hillside Hospital, Northwell Health, Glen Oaks, NY, USA; [e]Department of Psychiatry, Zucker School of Medicine at Northwell/Hofstra, Hempstead, NY, USA; [f]Department of Psychiatry, Psychotherapy and Psychosomatics, Hospital of Psychiatry, University of Zurich, Zurich, Switzerland

ABSTRACT

Objective: The aim of this review is to analyse the literature regarding studies centred on the clinical outcome of individuals affected by schizophrenia and treated with various antipsychotics, and then switched to orally administered partial D2-dopamine agonists (PD2A): Aripiprazole (ARI), brexpiprazole (BREX) or cariprazine (CARI).

Method: A PubMed literature search was performed on 16 February 2021, and updated on Jan 26, 2022 for literature on antipsychotic switching in individuals affected by schizophrenia. Literature was included from 2002 onward. Six strategies were defined: Abrupt, gradual and cross-taper switch, and 3 hybrid strategies. The primary outcome was all-cause discontinuation rate per switch strategy per goal medication.

Results: In 10 reports on switching to ARI, 21 studies with different strategies were described, but there were only 4 reports and 5 strategies on switching to BREX. Only one study about CARI was included, but it was not designed as a switch study. The studies are difficult to compare due to differences in methodology, previous antipsychotic medication, doses of the introduced P2DA and study duration.

Conclusion: This analysis did not reveal evidence for a preferable switching strategy. A protocol should be developed which defines optimal duration, instruments to be used, and the timing of the exams.

KEY MESSAGES

- Most switch studies on partial D2-agonists focus on ARI, with only a few on BREX, while little is known about the clinical outcome of switching individuals to CARI
- There is a wide variation of possible switch methods: Abrupt switch – gradual switch – cross-tapering switch – hybrid strategies including plateau switch
- The protocols used differ considerably between the studies. A strict comparison between the studies is difficult, for which reason the present evidence does not support an unambiguous preference for a particular switch strategy.
- From a methodological point of view, a standardised clinical protocol should be developed to allow comparisons between studies regarding the clinical outcome of individuals switched from one antipsychotic drug to another

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Partial D2-dopamine receptor agonists; antipsychotics; aripiprazole; brexpiprazole; cariprazine; switch; schizophrenia spectrum disease

Introduction

Antipsychotics are the main pharmacological treatment for individuals affected by schizophrenia. However, many individuals experience insufficient response or even relapse, intolerable side effects or poor tolerability on a given antipsychotic therapy, making a switch to a different antipsychotic necessary or desirable (Edlinger et al., 2005). Switching of antipsychotics is therefore often encountered in everyday clinical practice (Buckley & Correll, 2008; Chue et al., 2004; Edlinger et al., 2005; Ganguli, 2002; Hatta et al., 2018; Masand, 2005; Newcomer et al., 2013; Rossi et al., 2011; Takeuchi & Remington, 2020). Interestingly, many reviews on pharmacological switching strategies were published in a period when the replacement of first generation antipsychotics with second generation antipsychotics was considered advantageous. On the other hand, reviews on switching from any of these antipsychotics to the partial dopamine D2-agonists (PD2A) are rare (Citrome, 2015; Taylor et al., 2022). About 20 years ago, aripiprazole (ARI) was introduced as the first PD2A, followed by brexpiprazole (BREX) and cariprazine (CARI).

Similarly to other antipsychotics, PD2A reduce the activity of postsynaptic dopamine D2-receptors, but are in addition partial dopamine D2- and D3-agonists, resulting in low residual activity. As summarised by Mohr et al., 2021, ARI and CARI display the highest intrinsic D2- and D3-activity, respectively. These properties can explain the activating effect of ARI, while the hyperstimulation of D2- or D3-receptors can be responsible for several adverse effects such as akathisia, agitation, insomnia, but also for a reduced effect on prolactin secretion compared to many other antipsychotics. According to these authors, the reduced effect of BREX on these receptors results in a lower risk for the adverse effects mentioned, while its relatively high occupancy of

CONTACT Pierre Baumann pierre.baumann@unil.ch Private address: Chemin des Mainnesses 13, CH-1302 Vufflens-la-Ville, Switzerland

5-HT1a- and 5-HT2a-receptors, in comparison to ARI and CARI, explains its low risk for extrapyramidal symptoms. In comparison to most other available antipsychotics, for which central D2- and D3-receptor occupancy should be between 65% and 80% for optimal clinical efficacy, it should be > 90% for the three PD2A (Hart et al., 2022), as suggested by positron emission tomography (PET) studies in the human brain. Briefly, ARI, BREX and CARI are clinically effective antipsychotics (Citrome, 2015; Taylor et al., 2022) with a unique receptor profile, but direct comparative studies have not been carried out. A review and network meta-analysis (Pillinger et al., 2020) suggests that ARI, BREX and CARI cause fewer metabolic disturbances than most other antipsychotics, but another recent study which reports real-world data collected from 40 population-based studies concludes that, at least for BREX and CARI, insufficient data is available for such a statement (Bernardo et al., 2021).

The introduction of PD2A offered more possibilities for switching between antipsychotics, which differ as to their pharmacological mechanisms. While several studies report on switching from first or second-generation antipsychotics to ARI (Obayashi et al., 2020), the question arises whether similar studies have been carried out with BREX and CARI and whether the current evidence is sufficient to arrive at an optimal switching strategy for the three PD2As. A glance at product information published by different governmental organisations reveals that for ARI (Abilify ®), the American Food and Drug administration (FDA) document mentions (www.accessdata.fda.gov/drugsatfda_docs/label/2014/021436s038,021713s030,021729s022,021866s023lbl.pdf (accessed on December 1, 2022)): 'There are no systematically collected data to specifically address switching individuals with schizophrenia from other antipsychotics to ABILIFY or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some individuals with schizophrenia, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized'. The corresponding document from the European Medical Agency (EMA) does not recommend any switching strategy for this drug (www.ema.europa.eu/en/documents/product-information/abilify-maintena-epar-product-information_en.pdf (accessed on 1 December 2022)). On the other hand, the EMA published similar product information for BREX (https://www.ema.europa.eu/en/documents/product-information/rxulti-epar-product-information_en.pdf (accessed on 1 December 2022)) and CARI (https://www.ema.europa.eu/en/documents/product-information/reagila-epar-product-information_en.pdf (accessed on 1 December 2022)): 'When switching from another antipsychotic to cariprazine (respectively BREX) gradual cross-titration should be considered, with gradual discontinuation of the previous treatment while cariprazine (resp. BREX) treatment is initiated'.

Categories of switch strategies

Goals of switching are to avoid symptomatic worsening and relapse, while at the same time minimising the side effect burden. Principally, there are three basic switch strategies (Figure 1) for the discontinuation of a current medication (drug A) and its replacement by another antipsychotic drug (drug B) (Edlinger et al., 2005; Lambert, 2007; Rossi et al., 2011; Stahl, 2013), as also summarised in international and national guidelines (Barnes et al., 2020; Hasan et al., 2012; Kaiser et al., 2016). The definitions of the six different strategies are presented in Table 1 and depicted in Figure 1. Strategies 4–6 may be considered as variations or hybrids of strategies 1–3, as specified by arrows in Figure 1.

Advantages and disadvantages of the different switch strategies as well as their recommendation for particular clinical situations were summarised (Chue et al., 2004; Edlinger et al., 2005): Abrupt switching (strategy 1 – Figure 1A) presents a low risk of drug interactions, but withdrawal reactions are possible, whereby this strategy is claimed to be advantageous in individuals with serious adverse events. In contrast, gradual switching (strategy 2 – Figure 1B) could lead to a reduction in withdrawal reactions and drug interactions but could result in exacerbation

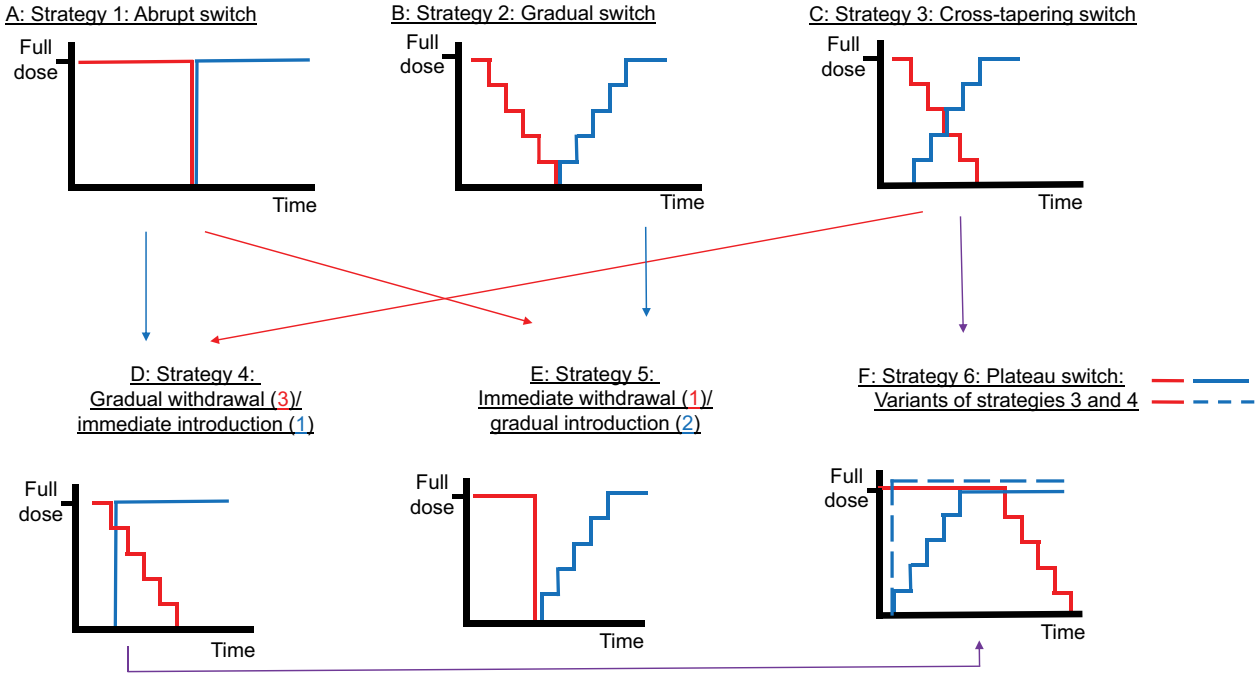


Figure 1. Switch strategies for withdrawal of drug A (red) and introduction of drug B (blue)

Table 1. Switching strategies from a treatment with antipsychotic drug A to antipsychotic drug B.

Strategy				
Nr	Characteristics	Drug A	Drug B	Figure
1	Abrupt switch	Immediate discontinuation	Immediate introduction at full dose	1 A
2	Gradual switch	Gradual discontinuation	Delayed introduction, and gradual dose increase	1B
3	Cross-taper switch (overlapping switch)	Gradual discontinuation	Immediate introduction, and gradual dose increase	1 C
4	Hybrid strategy: Gradual – immediate	Gradual discontinuation	Immediate introduction at full dose	1D
5	Hybrid strategy: Immediate – immediate/ gradual	Immediate discontinuation	Immediate introduction, and gradual dose increase	1E
6	Hybrid strategy: Plateau switch (also known as overlap and taper)	Full dose then gradual discontinuation	Gradual or immediate introduction	1F

of symptoms; it is recommended in individuals with low risk of relapse. This may be optimally prevented by cross-tapering (strategy 3 – Figure 1C), but this bears the risk of drug interactions. This strategy is recommended in recently stabilised individuals. Some guidelines (Hasan et al., 2012; Kaiser et al., 2016) generally do not recommend abrupt switching, but rather cross-tapering (strategy 3 – Figure 1C) and plateau switch (strategy 6 – Figure 1F).

Consultation of the so-called online platforms, e.g. antipsychotic switching tool (https://www.nps.org.au/australian-prescriber/articles/antipsychotic-switching-tool (accessed on 1 December 2022)) can aid in clinical decision-making, but does not answer the original question about the evidence of switch strategies from non-agonistic antipsychotics to PD2A. The question then arises whether the clinical outcome of the individuals regarding efficacy, safety and tolerability is favoured by a particular strategy.

Methods

This narrative review focused exclusively on studies including effectiveness and/or safety outcomes for switching from antipsychotics to orally administered ARI, BREX and CARI. It is based on a search that originally performed by one of the authors (Ph.B) on 16 February 2021 and updated on 26 January 2022 for literature in PubMed on antipsychotic switching in individuals affected by schizophrenia: Literature from 2002 onward, when the first partial dopamine D2 agonist ARI became available, was included. The list of referenced articles for more literature was also checked. Initially, search hits were scanned for articles with practical information on the switch process between antipsychotics for the treatment of adult patients affected by schizophrenia, in the form of expert opinions, randomised controlled trials (RCTs), or reviews and meta-analyses. Articles were excluded if the switch strategy was not the focus of the article (articles that compared efficacy and/or safety of the post-switch medication to that of the pre-switch medication), articles that discussed switching-related phenomena such as rebound, supersensitivity, withdrawal, or tardive dyskinesia without a focus on switch strategies, case reports, articles that discussed switching between different forms of administration of the same substance (e. g. oral to long-acting injectable or brand-name to generic), and articles that we could not readily assess for language reasons. For the final analysis, we (PB, PhB) chose to focus on original trial data reporting switches to PD2A. We therefore excluded literature that did not discuss switches to PD2A, articles in the form of reviews and expert opinions and secondary publications that presented post-hoc analyses of trial data. However, it appeared rapidly that regarding PD2A, studies which fulfil the conditions defined above for a switch study given above were only available for ARI and BREX, but not for CARI. Therefore, a CARI study was selected (PB) which partially fulfilled the conditions (cf below). The primary outcome was all-cause discontinuation rate per switch strategy per target medication, as a proxy for switch failure, and secondary outcomes were changes in Positive and Negative Syndrome Scale (PANSS) scores and other clinical scales.

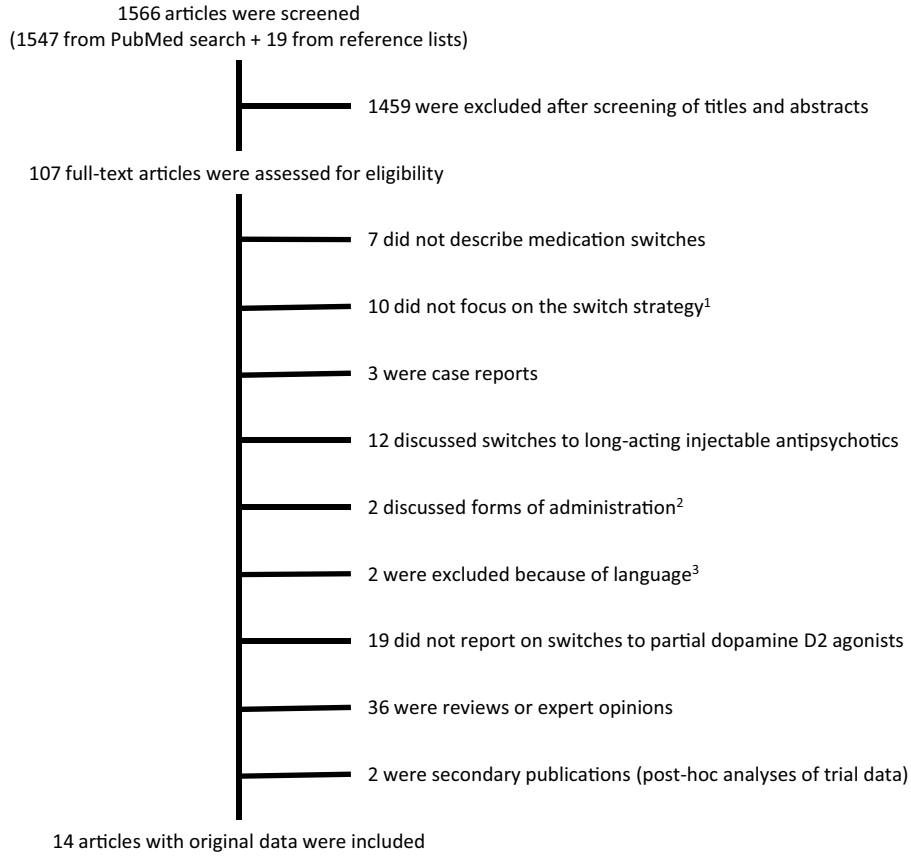
Results

In our search we identified 1547 articles, as well as 19 potentially eligible articles from reference lists. The literature flow is given in Figure 2. Information on antipsychotic switching strategies for PD2A was found in 14 articles.

Switch strategies in studies with PD2A as drug B

Drugs A comprise a large variety of first and second generation antipsychotics (except previous medication with clozapine, which is excluded in most studies), but there are only 10 and 4 reports listing ARI or BREX as drug B respectively, and most of them, mainly ARI studies, are comparisons between different strategies. There is only one investigation (Nemeth et al., 2017), which describes the switching strategy to CARI, whereby however no comparative data are communicated on the clinical evolution of the patients before and after the switch. There is no study that fulfils the criteria valid for category A of empirical evidence (positive evidence from controlled studies (e.g. double-blind)) (Bandelow et al., 2008). Only a few studies respond to some criteria of category B (limited positive evidence from controlled studies), but none contained a placebo arm. Indeed, switch studies are generally open studies. Exceptions are an ARI study, where raters, but not the participants and treating physicians, were blinded to treatment assignment (Stroup et al., 2011), and the double blind CARI investigation mentioned above (Nemeth et al., 2017).

Despite the 3 antipsychotics share many similarities in their pharmacological profile and pharmacokinetic properties, characterised by relatively long elimination half-lives (Hiemke et al. 2018; Schoretsanitis et al., 2020), there are some differences regarding the strategies used (Tables 2 and 3). While strategy 3 (Figure 1C) was most often tested, in the case of ARI, the hybrid strategy 4 (Figure 1D) was also frequent. This means that the authors did not hesitate to introduce ARI abruptly, at full dose (Casey et al., 2003; Hwang et al., 2015; Lin et al., 2009; Ryckmans et al., 2009). This strategy was not described for BREX, as only cross-tapering switch (strategy 3 – Figure 1C) and its variant, plateau switch (strategy 6 – Figure 1F), were tested. The only study with CARI as drug B comprised cross-tapering switch (strategy 3 – Figure 1C). The hybrid strategy 5 (Figure 1E) was tested in only two ARI studies (Lin et al., 2009; Obayashi et al., 2020).



[1] focus was on better efficacy and/or safety of post-switch medication compared to pre-switch medication, not on optimal transition strategy
[2] Switching forms of administration for the same substance, e. g. oral formulation to LAI, or brand-name to generic
[3] Danish, Japanese

Figure 2. Literature search flow.

Switch studies on ARI

Regarding orally administered ARI (drug B), with 21 strategies described in 10 reports, there are only two studies about an abrupt switch (strategy 1 – Figure 1A) (Casey et al., 2003; Obayashi et al., 2020). None of the clinical studies is based on a gradual switch (strategy 2 – Figure 1B), but a cross-taper (overlapping) switch (strategy 3 – Figure 1C) was chosen 7 times (Casey et al., 2003; Chen et al., 2012; Kim et al., 2009; Obayashi et al., 2020; Pae et al., 2009; Ryckmans et al., 2009; Takeuchi et al., 2008), and once in a slightly modified form (delayed tapering off of drug A, as explained below) (Pae et al., 2009). A plateau switch (strategy 6 – Figure 1F) was carried out in 5 groups of patients (Hwang et al., 2015; Obayashi et al., 2020; Stroup et al., 2011; Takeuchi et al., 2008) in 4 reports, because in one study, tapering off of drug A was either fast or slow (Hwang et al., 2015). Hybrid strategies were examined 6 times: the hybrid strategy 4 (Figure 1D) (Casey et al., 2003; Lin et al., 2009; Ryckmans et al., 2009) and the hybrid strategy 5 (Figure 1E) (Lin et al., 2009; Pae et al., 2009);(Obayashi et al., 2020). All ARI studies include several arms, which allows for direct comparison of some strategies. In the following subsections, it will be considered that in some studies, comparisons are made between switch strategies, while others are centred on the biological consequences of a switch to ARI.

Study 1 (Table 2): In the 3-arm, open and 8-week multicentre study of (Casey et al., 2003), ARI treatment led to continuous improvement as measured with the PANSS and the both versions of the Clinical Global Impression (CGI) Rating Scale (Improvement (CGI-I) and Severity (CGI-S)), but no statistical analysis was reported. Adverse effects were recorded by questioning and the Simpson-Angus scale (SAS), Barnes Akathisia Rating Scale (BAS) and Abnormal Involuntary Movement scale (AIMS). Non information was provided regarding comedications. The discontinuation rate was somewhat lower in group 3 (19%), characterised by a cross-tapering switch (strategy 3 – Figure 1C) of the medications, in comparison to that observed in group 1 after an abrupt switch (strategy 1 – Figure 1A) (31% discontinuation) or in group 2, with a hybrid strategy (strategy 4 – Figure 1D) (34% discontinuation). The incidence of adverse effects (means: 81–89%) was similar in the 3 groups, as was that of a severe adverse event leading to hospitalisation. There were some group differences with respect to occurrence of diarrhoea, upper respiration infection, nausea and vomiting, but no clear trend was evident that could allow for designation of a strategy as a particularly risky procedure: In group 1, the incidence of diarrhoea was lower than in groups 2 and 3, that of respiratory infection was higher in group 2 and that of nausea and vomiting were lower in group 3. Movement disorders showed a tendency to slight improvement while there was a slight decrease in body weight in all 3 groups (means: between −1.3 kg and −1.7 kg). In all groups there was a higher percentage of patients who lost ≥ 7% weight than of those who gained ≥ 7% weight. Mean changes of prolactin (between 15.9 ng/mL and 19.4 ng/mL) and of QTc (between −3.58 msec and −6.94 msec) were also similar in all groups. Therefore, the authors concluded that switching patients from prior antipsychotic treatments

to ARI can be achieved successfully with any of the 3 strategies (Casey et al., 2003), but they did not separately analyse the possible consequences of a discontinuation of risperidone vs olanzapine while switching to ARI.

Study 2 (Table 2): In the randomised open-label, parallel group 14-week study in individuals affected by schizophrenia reported by (Takeuchi et al., 2008), cross-tapering switch (non-wait group) (strategy 3 – Figure 1C) or its variant, plateau-switch (wait group) (strategy 6 – Figure 1F) did not result in clear differences in the clinical outcome of patients in whom previous antipsychotics were discontinued and ARI introduced. Clinical rating scales used were the following ones: Subjective Wellbeing Under Neuroleptics, Short Version, Japanese Edition (SWNS-J), CGI-schizophrenia version, Global Assessment of Functioning (GAF), and a questionnaire about the subjects' attitudes towards switching strategy, while adverse effects were rated with the BAS and the Drug Induced Extrapyramidal Symptoms scale (DIEPSS). With regard to comedications, stable (mood stabilisers, benzodiazepines) treatment was allowed, but no CYP2D6 inhibitors, no CYP3A4 inhibitors or substrates, and no selective serotonin reuptake inhibitors (SSRI). Additional medications were allowed for the management of conditions (adverse effects, new intercurrent illness). Only one patient (4%) of the wait group ($n = 26$) and 4 patients (15%) of the non-wait group ($n = 27$) discontinued treatment. In both groups, significant reduction of body weight, cholesterol, triglycerides, prolactin and QTc was observed. The authors concluded that both strategies are objectively safe and well tolerated, and that therefore the choice of the strategy should include consideration of a patient's preference.

Study 3 (Table 2): In this prospective randomised open-label, multicentre 12-week study, a group of individuals affected by schizophrenia or schizoaffective disorder and treated with antipsychotics was submitted to a cross-tapering switch to ARI (strategy 3 – Figure 1C), while the patients of another group were switched to another treatment with various other antipsychotics (Kim et al., 2009). The following clinical instruments were used: PANSS, CGI, Investigator's Assessment Questionnaire (IAQ), Udvalg for Kliniske Undersogelser side-effect rating scale (UKU), Treatment-emergent adverse events (TEAE), and serious adverse events (SAE) were recorded. Benzodiazepines (55.7%), anticholinergics (39.6%), β-blockers (15.2%), mood stabilisers (11.3%), and antidepressants (10.0%) were concomitantly administered in the ARI-group. Patients switched to ARI showed some greater improvement on some scales (CGI-S, positive symptoms PANSS), but not on the total score of PANSS. In the ARI group, there was a higher but statistically not significant (ns) discontinuation rate (38%) in comparison to the group submitted to 'standard of care' with other antipsychotics (27.7%) and a considerably higher occurrence of some adverse effects such as insomnia, nausea and headache. As expected, prolactin elevation was lower in ARI-treated patients. In both groups, a significant reduction in body weight, cholesterol, triglycerides, prolactin, and in the QTc interval occurred. In clinically stable patients, most of them were successfully switched to ARI without exacerbation of symptoms or occurrence of severe adverse effects.

Study 4 (Table 2): In a 12-week observational study, Lin et al. (2009) switched the current treatment of individual suffering from schizophrenia with antipsychotics to ARI, mainly because of adverse effects characterised by metabolic problems or abnormal endocrine functions (Lin et al., 2009). Two different hybrid switch strategies were used: Strategy 5 (Figure 1E) or strategy 4 (Figure 1D). Only the CGI-S scale was used and the differential effect of the strategies on the clinical outcome of the patients was not communicated, as the analysis was centred on completers and non-completers, and not on differences in efficacy between the switch strategies. Discontinuation rates were lower in patients submitted to abrupt discontinuation (21.4%) than in those submitted to graduate tapering (35.5%) (Table 2). The average daily dose of ARI reached 11.1 ± 6.7 mg and 10.4 ± 3.1 mg in completers and non-completers, respectively. No specific rating scale for adverse effects was used. Less than 30% of the subjects complained about adverse effects after introduction of ARI, and the only adverse effect present in more than 10% of the patients was insomnia (17.8%). The lowest success rate in switching was observed in patients where first generation antipsychotics were the previous antipsychotic medication, but regarding second generation antipsychotics, difficulties in switching occurred particularly with olanzapine, clozapine, and quetiapine (probably related to their anticholinergic properties), whereby insomnia, anxiety, extrapyramidal side effects (EPS) and akathisia were sometimes observed.

Study 5 (Table 2): In all 3 groups of patients who participated in a randomised open-label 12-week study, there was an immediate initiation of 10 mg/day ARI, which was then flexibly adjusted within 10–30 mg/day during the whole study period (Pae et al., 2009). Instruments for the clinical exams of the patients comprised the CGI, the Brief-psychiatric rating scale (BPRS) scales and the Schedule for the assessment of negative symptoms, while adverse effects were recorded with the SAS, BAS, AIMS, and the Systematic assessment for treatment emergent events (SAFTEE). No information is available regarding authorised comedication. The groups of patients differed as to the way the preceding treatment with different antipsychotics was discontinued: In group 1, submitted to strategy 5 (Figure 1E), switching to ARI after an immediate discontinuation of a previous treatment with different antipsychotics resulted in an increase of symptom severity at week 1 (but not in severity of side effects). The patients of groups 2 and 3 were subjected to a cross-tapering switch (strategy 3 – Figure 1C), the main difference being that discontinuation times were 4 and 6 weeks, respectively. The authors (Pae et al., 2009) then concluded that a stepwise reduction of drug A should be preferred to its abrupt discontinuation. This pejoration in group 1 occurred despite the inclusion criteria that patients should be selected because of poor clinical effect or poor tolerability of the first treatment. Discontinuation rates did not differ significantly between the groups, but were highest in group 1 (74%), that is in patients submitted to an abrupt discontinuation of drug A and a gradual increase of ARI doses. Groups 2 and 3 had discontinuation rates of 48% and 44%, respectively. Dropouts occurred mainly during the first 6 weeks of ARI treatment. Unfortunately, no data are available on prescribed ARI doses during the first weeks, it being stated only that ARI treatment was commenced with 10 mg/day, but that flexible doses (10–30 mg/day) were then allowed during the entire treatment period. Therefore, underdosage of ARI cannot be excluded, especially in patients where drug A was abruptly discontinued.

Study 6 (Table 2): A comparative, randomised, multicentre and open-label 12-week study with a comparatively high number of subjects affected by schizophrenia responding insufficiently to risperidone or showing poor tolerability/safety was realised by Ryckmans et al. (2009). Clinical ratings were carried out with – PANSS, – CGI, – a cognition scale developed by the Grupo Español para la Optimización y Tratamiento de la Esquizofrenia (GEOPTE cognition scale), – the Impact of weight on Quality of life scale (IWQoL-Lite), and – the Arizona sexual experience scale (ASEX), while adverse effects were recorded with the SAS. Rescue benzodiazepines (< 4 mg/day) and antiparkinsonian medications for acute extrapyramidal symptoms were allowed. In group 1 ($n = 200$)

Table 2. Switching from a treatment with antipsychotics (drug A) to ARI (drug B) using different strategies.

Study (Nr)	Study type (duration)	Sample diagnosis	Reasons for switching	Previous antipsychotic medication	Discontinuation strategy	Switching strategy	Efficacy	Adverse effects	Discontinuation rate (n: total number of included patients)
Casey et al., (2003) (1)	Open multicentre study (8 weeks)	(Chronic) schizophrenia, schizoaffective disorder (DSM-IV) (Stable for at least 1 month before switch. No hospitalisation for an exacerbation for at least 2 months)	Adequate clinical reason for trying a new antipsychotic drug (i.e. ARI) other than current therapy (no details communicated)	For at least one month before switch: Olanzapine and risperidone (92%); haloperidol (5%), other typical AP (3%) (doses not precised)	Group 1: Immediate discontinuation	Group 1 (Strategy 1 – Figure 1A): Immediate initiation (30 mg/day ARI, single morning dose)	All 3 switching strategies: Favourable efficacy: Improvements in both positive and negative symptoms	All 3 switching strategies: Favourable safety and tolerability (EPS)). Most frequent AE: mild to moderate insomnia: Groups 1–3: 28% – 33%. Nausea (11–22%) and vomiting (2–12%): Lower in group 3 than in groups 1 (22%) and 2 (22%). Akathisia (mostly, low to moderate): Higher in group 3 (21%) than in groups 1 (15 %) and 2 (11%). SAE (hospitalisation): 7% (mostly worsening of schizophrenia)	Group 1 ($n = 104$): 31%
					Groups 2 and 3: Tapering off current AP treatment over the first 14 days (i.e. week 1: decrease of the dose to 50% of the previous week; 2nd week: decrease of the dose to 50 % of week 1; start of week 3: total discontinuation)	Group 2 (Strategy 4 – Figure 1D): Immediate initiation (30 mg/day ARI, single morning dose)			Group 2 ($n = 104$): 34%
						Group 3 (Strategy 3 – Figure 1C): Uptitrating of ARI: 1st week: 10 mg/day; 2nd week: 20 mg/day; 3rd week: 30 mg/day over 2 weeks			Group 3 ($n = 103$): 19%
Takeuchi et al., (2008) (2)	Randomised open-label, parallel group study (14 weeks)	Schizophrenia (DSM-IV)	n.a.	Risperidone, olanzapine and others	Group 1 (Wait group): Subsequent tapering of previous AP (biweekly by 25%) after 4 weeks ARI treatment	Group 1 (Strategy 6 – Figure 1F): Immediate add-on ARI (12 mg/day during 2 weeks), then titration between 12 and 30 mg/day	No clear differences between groups, and between baseline and endpoint	Group 1: Insomnia: 19%	Group 1 ($n = 26$): 4%
					Group 2 (No-wait group): Tapering of previous AP (biweekly by 25%)	Group 2 (Strategy 3 -m Figure 1C): Immediate add-on ARI (12 mg/day during 2 weeks), then titration between 12 and 30 mg/day		Group2: Insomnia: 26%	Group 2 ($n = 27$): 15%
Kim et al., (2009) (3)	Prospective randomised open label multicentre study (12 weeks)	Schizophrenia, schizoaffective disorder (DSM-IV)	Weight gain, inadequate control of symptoms, somnolence	Risperidone, olanzapine and others	Group 1: Gradual discontinuation of AP pre-treatment during the first 2 weeks	Group 1 (Strategy 3 – Figure 1C): 10 mg/day ARI, immediately, then adjustement (10–30 mg/day) (investigator's judgement)	Group 1: Improvement score (CGI-improvement), at 12 weeks: 3.56 ± 1.29. Some superior clinical effect in group 1 vs group 2 (CGI-S (severity) score, PANSS (positive subscale), remission rate.	TEAE: Group 1 vs group 2: 25.6 % vs 4.4 % (insomnia); 16.5 % vs 4.4% (nausea); 10.4 % vs 4.4% headache).	Group 1 ($n = 245$): 38%
					Group 2: Standard of care (switch to non-partial D2-agonists AP)	Group 2: no switch to partial D2-agonist AP			Group 2 ($n = 47$): 27.7%

Lin et al., 2009 (4)	Observational study (12 weeks)	Schizophrenia (DSM-IV)	Metabolic problems (53.3%) , hyperprolactinaemia (20%), drug efficacy (13.3%), EPS (11.1%), others	Mainly second generation AP (82.2 %) (doses not precised)	Group 1: Abrupt discontinuation	Group 1 (Strategy 5 – Figure 1E): Immediate ARI introduction but no information on dose titration	Clinical scores separately presented only for completers vs non-completers, and not according to switching procedure (group 1 vs group 2)	42.9% of the non-completers terminated treatment in the first 2 weeks of treatment. AE (in all patients): Insomnia:17.8%; anxiety: 8.9%, etc	Group 1 ($n = 14$): 21.4%
					Group 2: Graduate tapering	Group 2 (Strategy 4 – Figure 1D): Immediate ARI introduction but no information on ARI dose titration			Group 2 ($n = 31$): 35.5%
Pae et al., (2009) (5)	Randomised open-label study 12 weeks)	Schizophrenia (DSM-IV)	Insufficient efficacy or poor tolerance to current AP treatment	Risperidone, olanzapine, amisulpride, quetiapine	Group 1: Immediate discontinuation	All groups: 10 mg/day ARI immediately, then flexible adjustment (10–30 mg/day). Group 1: Strategy 5 – Figure 1E)	Group 1: Increase of severity (CGI-S) during week 1. Week 2: CGI-S (severity) (group 1) > CGI-S (groups 2 and 3 joined together). Week 4: No difference	No difference between groups regarding AE (headache, anxiety, insomnia, etc)	Group 1 ($n = 31$) 74%
					Group 2: Tapering off current AP treatment over the first 28 days (i.e. half of the dose after the first 2 weeks)	Group 2: Strategy 3 – Figure 1C			Group 2 ($n = 29$): 48%
					Group 3: Tapering off current AP treatment over the first 28 days, after maintenance of current dose for 2 weeks	Group 3: Strategy 3 – Figure 1C			Group 3 ($n = 27$): 44%
Ryckmans et al., (2009) (6)	Comparative, randomised, multicentre, open-label study (12 weeks)	Schizophrenia (DSM-IV-TR)	Insufficient efficacy and/or safety/tolerance issues	Risperidone	Groups 1 and 2: Tapering risperidone (week 1 and 2: current treatment; weeks 3 and 4: 50 % dose; week 5: 0 mg/day)	Group 1 (Strategy 3 – Figure 1C): ARI titration: week 1: 5 mg/day; week 2 and 3: 10 mg/day; week 4–5: 15 mg/day; after week 5: 10–30 mg/day)	Week 12 vs baseline: Similar marked improvement in PANSS scores: Group 1: – 14.8; group 2: – 17.2	No AE with a frequency > 10%.	Group 1 ($n = 200$): 3.5%
						Group 2 (Strategy 4 – Figure 1D): ARI fixed dose (weeks 1–5: 15 mg/day; then 10–30 mg/day)			Group 2 ($n = 200$): 5%
Stroup et al., (2011) (7)	Randomised controlled multicentre study (24 weeks)	Schizophrenia, schizoaffective disorder	Metabolic profile: Increased risk for cardiovascular disorders	5–20 mg/day, olanzapine, 200–1200 mg/day quetiapiine, 1–16 mg/day risperidone	Group 1: Week 1: Current treatement for 1 week, at the same doses; week 2: dose reduction 25–50%; after 3 weeks: medication stopped	Group 1 (Strategy 6–Figure 1F): Week 1: Initiation with 5 mg/day ARI ; week 2: 10 mg/day; week 3: 15 mg/day if needed; after 3 and 4 weeks: 5–20 mg/day and 5–30 mg/day, respectively	Groups 1 and 2: Similar decrease in PANSS- (– 5.0 vs –3.9) and CGI-S scores. Decrease of SF-12 physical health and IWQoL scores: Group 1 > group 2	Moderate or severe AE (24 weeks, > 20 %: observed in both groups separately): Insomnia, sleepiness, dry mouth, akathisia/activation, problems with sex drive.	Group 1 ($n = 109$): Within 1 month (within 24 weeks): 16.8% (47.7%) ($p < 0.001$)
					Group 2: Continuation of current treatment	No switch			Group 2 ($n = 106$): 7.5% (27.4%)

(*Continued*)

Table 2. Continued.

Study (Nr)	Study type (duration)	Sample diagnosis	Reasons for switching	Previous antipsychotic medication	Discontinuation strategy	Switching strategy	Efficacy	Adverse effects	Discontinuation rate (n: total number of included patients)
Chen et al., (2012) (8)	Prospective, randomised, open-label study (12 months)	Schizophrenia, schizoaffective or bipolar disorder (DSM-IV-TR)	Risky metabolic profile	Mainly quetiapine, risperidone, olanzapine	Groups 1 and 2 : Discontinuation within 2 weeks	Groups 1 and 2: Target dose reached within 2 weeks (investigator's judgement). Group 1: (Strategy 3 – Figure 1C) 5–30 mg/day ARI. Group 2: (Strategy 3 – Figure 1C) 40–160 mg/day ZIPR	Time or group × time interaction effects for YMRS, CGI-S or PANSS total or subscale scores: ns. Changes in any of these measures from baseline were observed in either treatment group: ns	Group 1 (12 months): no patient discontinued treatment because of adverse effects. AE: insomnia ($n = 9$), nausea/ gastrointestinal upset ($n = 4$), nervousness/anxiety ($n = 5$), tremor ($n = 4$)	Group 1 ($n = 24$): 33% (6 months) Group 2 ($n = 28$): 32% (6 months) (ziprasidone)
Hwang et al., (2015) (9)	Open-label, randomised, parallel study (8 weeks)	Schizophrenia, schizoaffective disorder (DSM IV) (chronic and stable)	Inadequate efficacy or adverse effects of the current medication	Sulpiride, flurazine, haloperidol, olanzapine, risperidone, amisulpride and others	Group 1 (Fast tapering): Within 1 week after initiation of ARI treatment for 2 weeks Group 2 (Slow tapering): Within 4 weeks (approx. 25%/week) after initiation of ARI treatment for 2 weeks	Groups 1 and 2: (Strategy 6 – Figure 1F) immediate full dose (15 mg/day) ARI, given as a single morning dose	In both groups, significant decrease in total, negative and general psychopathology PANSS scores, but not in positive PANSS scores. Any PANSS score: no difference between groups,	EPS: no time-by-group interaction. BAS score: Higher in group 2 than in group 1	Group 1 ($n = 26$): 23.7% Group 2 ($n = 27$): 43.9% ($p < 0.1$: group 1 vs group 2)
Obayashi et al., (2020) (10)	Historical multicentre cohort study (real clinical practice) (6 months)	Chronic schizophrenia	Psychiatric symptoms, adverse effects, both	Risperidone ($n = 72$), olanzapine ($n = 51$), and others ($n = 43$), and combination therapy ($n = 12$)	Group 1 : Add-on switching: Previous AP treatment was not changed for at least one week. Then, previous AP was tapered off	Groups 1–3: ARI dose at start and target: flexible (clinical judgement). Group 1 (Strategy 6 – Figure 1F): During tapering off of previous AP, ARI was started for a 6-month treatment; starting dose: 8.62 ± 6.42 mg/day	Groups 1–3: Improvement (CGI score change): Group 1: in 66.7% patients; group 2: 56.5%; group 3: 46.5%	Group 1: adverse reactions in 28.9% patients; EPS: in 20% patients	Group 1 ($n = 45$): 28.9%
					Group 2 : Cross switching: Tapering off previous AP	Group 2 (Strategy 3 – Figure 1C): During tapering off previous AP, ARI (dose at start and target: flexible) treatment was started for a 6-month treatment; starting dose: 11.2 ± 6.43 mg/day	Group 2: 56.5%	Group 2: Adverse reactions: 21.0%; EPS: 12.9%	Group 2 ($n = 62$): 41.9%
					Group 3: Direct switching: Immediate stop of previous AP treatment	Group 3 (Strategy 1 – Figure 1A, or strategy 5 – Figure 1E): ARI was started immediately (dose at start and target: flexible); starting dose: 9.99 ± 6.55 mg/ day	Group 3: 46.5%	Group 3: Adverse reactions: 16.9%. EPS: 7%	Group 3 ($n = 71$): 53.6%

Abbreviations: AP: Antipsychotics; ARI: Aripiprazole; ZIPR: ziprasidone.
Ratings: AE: Adverse effects; BAS: Barnes Akathisia rating scale; CGI: Clinical Global Impression scale; CGI-S (severity); IWQoL: Impact of weight on Quality of life; PANSS: Positive and negative symptoms scale; SAE: Serious adverse events; TEAE: Treatment-emergent adverse events.
n.a.: not available; ns: not significant.

Table 3. Switching from a treatment with antipsychotics (drug A) to BREX or CARI (drug B) using different strategies.

Study (Nr)	Study type (duration)	Sample diagnosis	Reasons for switching	Previous antipsychotic medication	Discontinuation strategy	Switching strategy	Efficacy	Adverse effects	Discontinuation rate (n: total number of included patients)
Brexpiprazole (BREX)									
Correll et al. (2019) (11)	Open label (8 weeks)	Schizophrenia (DSM-IV)	Acute exacerbation of psychotic symptoms (PANSS total score > 80)	> 10 % of the patients: Risperidone > olanzapine > quetiapine > haloperidol > aripiprazole	Group 1–4: Length of tapering phase (conversion time): Group 1: 1–7 days Group 2: 8–14 days Group 3: 15 –21 days Group 4: 22–33 days	Groups 1–4: Strategy 3: Cross tapering switch (Figure 1C). Initiate on 1 mg/day BREX, then adjust 1–4 mg/day BREX over 1–4 weeks (investigator's judgement), while gradually reducing the dose of other antipsychotic	292/ 404 (72.3%) patients: conversion to BREX and completion of 8-week study: Group 1: 2.4% ; group 2: 6.5%; group 3: 11.0%; group 4: 80.1%. No difference in improvement in total PANSS or CGI-S scores from baseline	TEAE ($n = 404$): Insomnia: 11.1%; Headache: 7.2%, agitation: 6.2%; akathisia: 5.2%	Patients who received at least one BREX dose in the conversion phase ($n = 404$): 13.4%
Ichinose et al., (2021) (12)	Open label study (8 weeks) (improvement of side effects)	Schizophrenia, schizoaffective disorder (DSM-V)	Side effects: extrapyramidal symptoms, weight gain, hyperglycaemia, hyperlipidaemia, hyperprolactinaemia, etc	> 10 % of the patients: Risperidone, blonanserin, olanzapine or paliperidone *	Groups 1 and 2: Gradual discontinuation	Groups 1 and 2 together: BREX dose not fixed (at endpoint: 1.9 ± 0.3 mg/ day). Group 1: Strategy 6 – Figure 1F Group 2: Strategy 3 – Figure 1C	PANSS total score, CGI-S: No significant changes (baseline vs endpoint)	DIEPSS: significant decrease ($p = 0.008$). Body weight and BMI: significant decreases	Groups 1 ($n = 24$) and 2 ($n = 13$): 27% (includes worsening of schizophrenia: ($n = 10$); irritation ($n = 2$); insomnia ($n = 2$))
Ishigooka et al., (2020) § (13)	Open label study (8 weeks) as part of a longterm study (52 weeks)	Schizophrenia	Need for chronic antipsychotic treatment (investigator's opinion); considered for monotherapy with BREX	> 5 % of the patients: Aripiprazole ($n = 82$), olanzapine, risperidone or paliperidone	Constant dose treatment with current AP during 2 weeks, followed by its tapering off during 2 weeks	Strategy 6 – Figure 1F: Immediate initiation of BREX. Weeks 1 and 2: 1 mg/ day; weeks 3 and 4: 1–2 mg/ day; week 5: 1–3 mg/day; weeks 6 and 7: 1–4 mg/day	No substantial change in PANSS total score, from baseline till week 8	During this phase, no notable change in AE, except decrease of nasopharingitis (from 9.5% to 6.1%)	Whole group ($n = 200$): 17.0% (Consent withdrawal: 9.5%; adverse events: 5.5%; etc). Discontinuation rate during the 4-week-switch and 4-week post-switch phase: 9.5% and 8.3%, respectively.

(*Continued*)

Table 3. Continued.

Study (Nr)	Study type (duration)	Sample diagnosis	Reasons for switching	Previous antipsychotic medication	Discontinuation strategy	Switching strategy	Efficacy	Adverse effects	Discontinuation rate (n: total number of included patients)
Ishigooka et al., (2021) § (14)	Open label study (8 weeks) as part of a longterm study (52 weeks)	Schizophrenia	Need for chronic antipsychotic treatment (investigator's opinion); considered for monotherapy with BREX	Only atypical AP (except clozapine). Aripiprazole ($n = 82$); other atypical AP: $n = 104$ (risperidone (33), paliperidone (16), olanzapine (36), quetiapine (8))	Constant dose treatment with current AP during 2 weeks, followed by its tapering off during 2 weeks	Strategy 6 – Figure 1F: Immediate initiation of BREX. Weeks 1 and 2: 1 mg/day; After 2 to 3 weeks: 2 mg/day (4-week switch period), then 1–4 mg/day	From baseline to week 56: Small decreases in the PANSS- and CGI-S scores	Most common TEAEs: Nasopharyngitis, schizophrenia, headache, akathisia, etc	Whole group ($n = 186$): 45.2% (32.9% ARI subgroup; 54.8% other AP (consent withdrawal: 20.7 % (ARI), 27.9% (other AP); AE: 8.5% and 15.4%, respect., exacerbation of schizophrenia (6.1% and 12.5%, respect.))
Cariprazine (CARI)									
Nemeth et al., (2017) (15)	Phase II/III clinical study (26 weeks)	Schizophrenia, predominent negative symptoms	High PANSS-FSNS score	n.a.	Tapering off of current AP within the first 2 (- 4) weeks	Strategy 3 – Figure 1C. Immediate uptitration of CARI: days 0–6: 1.5 mg/day; days 7–13: 3 mg/day; Day 14: target dose: 4.5 mg/day	n.a. for the 2 (- 4) –week switch phase	n.a. for the 2 (- 4) –week switch phase	Whole group: $n = 227$: Uptitration phase (2 (- 4) –weeks)): CARI: 4%; risperidone: 2%

AP: Antipsychotics; BREX: Brexpiprazole; CARI: Cariprazine.
Ratings: AE: Adverse effects; CGI: Clinical Global Impression scale; CGI-S (severity); DIEPSS: Drug Induced Extrapyramidal Symptoms scale ; PANSS: Positive and negative symptoms scale; TEAE: Treatment-emergent adverse events.
n.a.: not available; §: These 2 studies are parts from the same clinical trial (NCT 01456897).

and in group 2 ($n = 200$), current treatment with risperidone was progressively decreased to reach complete discontinuation at week 5. The authors then compared the consequences of a cross-tapering switch (strategy 3 – Figure 1C) carried out in group 1 (5 mg/day at week 1, final dose at week 5: 15 mg/day ARI) with those of a hybrid switch (strategy 4 – Figure 1D) introduced in group 2 (5 mg/day ARI). These careful procedures may explain the extremely low discontinuation rates (group 1: 3.5%; group 2: 5%). The 12-week treatment with ARI led to a similar clinical effect of the strategies in both groups, with a significant improvement as shown by the PANSS and CGI scores. Both strategies resulted in a similar decrease in body weight (group 1: 1.4 kg; group 2: 1.3 kg) and prolactin levels (48%: similar in both groups).

Study 7 (Table 2): The principal aim of this following randomised and controlled multicentre 24-week study (Stroup et al., 2011) was to examine the evolution of metabolic parameters in individuals suffering from schizophrenia or schizoaffective disorder and currently treated with olanzapine, quetiapine or risperidone, and then switched to ARI (group 1), using the 'plateau switch' (strategy 6 – Figure 2F), while the current treatment in group 2 was continued (Table 2). Patients to be included had a body mass index (BMI) ≥ 27 and non-HDL cholesterol ≥130 mg/dL. The clinical raters of symptoms measured with the instruments PANSS, CGI, AIMS, BAS and SAS were blinded to treatment assignment. Patients taking stable doses of lithium, valproate, or lipid-lowering medications at the time of study entry could continue these treatments, but dose adjustments were not allowed during the treatment period, During the trial, the introduction of lithium, valproate, lipid-lowering agents such as statins, or drugs prescribed for weight loss was not allowed. All other medications, except for non-study antipsychotics, were allowed. Switchers lost more weight (-3.6 kg) than non-switchers (-0.7 kg), and the BMI reduction was higher in the former group. The change in non-HDL cholesterol (least squares means) was significantly more pronounced in the switch than the stay group (-20.2 mg/dL compared with −10.8 mg/dL), while there were no significant differences between the treatment groups in changes in HDL or low-density lipoprotein (LDL) cholesterol. On the other hand, the changes in triglyceride levels differed significantly between the groups: in the switch group there was a decrease (-25.7 mg/dL) and an increase (+7.0 mg/dL) in the other group. About one patient out of five in both groups experienced treatment failure. There were no differences between the groups regarding the evolution of PANSS scores and CGI. However, before 1 month had elapsed, 16.8% of the patients of the ARI group discontinued treatment, while only 7.5% of the non-switchers did so. In 47.7% and 27.4% of the switchers and non-switchers, respectively, the protocol-specified treatment was stopped before 24 weeks were complete ($p = 0.0019$). This suggests that, regarding metabolic problems, a switch to ARI may be an advantage, but that efforts should be centred on avoidance of treatment discontinuation.

Study 8 (Table 2): In a small prospective, randomised and open-label 12-month study in subjects presenting with schizophrenia, schizoaffective or bipolar disorder, the clinical consequences of a cross-tapering switch (strategy 3 – Figure 1C) from a current antipsychotic treatment to ARI (5–30 mg/day) or ziprasidone (40–160 mg/day) were examined (Chen et al., 2012). At baseline, week 26 and week 52, ratings were performed with the rating scales PANSS, Young-Mania Rating Scale (YMRS), HAM-D, Qualitiy of life scale (QLS), for efficacy, and with BAS, SAS, AIMS, for adverse effects. Comedications such as benzodiazepines, anticholinergics, antidepressants and mood stabilisers were allowed. At 6 months, 71.2% of the patients had completed all study visits. None of the patients discontinued ARI treatment because of adverse effects. As measured with the clinical rating scales, there was no pejoration or amelioration of the clinical situation regarding efficacy of either drug B, except that in the ARI group significant improvement in GAF scores from baseline was observed at 26 and 52 weeks. The study was focused on the evaluation of metabolic parameters measured in patients who, at inclusion, had a triglycerides/HDL ratio of ≥ 3.5 in fasting conditions. At baseline, triglycerides were elevated in both groups, and after switching there was a significant decrease in this parameter and in the ratio in both groups as mentioned at week 6. However, at week 52, only 16.7% and 21.4% of ARI and ziprasidone-treated patients had a triglycerides/HDL ratio < 3.5. In body weight, BMI, triglycerides and HDL there were statistically significant improvements, but they did not differ between treatments. Interestingly, and this was only observed in the ARI group, there were significant reductions of HgA1c levels over time. Compared to baseline, there was a trend at week 12, followed by further and significant improvements at 26 and 52 weeks.

Study 9 (Table 2): In another, open-label randomised, parallel 8-week study centred on the clinical consequences of fast (group 1) vs slow (group 2) tapering of current antipsychotic therapy (Hwang et al., 2015), drug B (ARI) was immediately given in a full dose (15 mg/day). This strategy can be considered a plateau switch (strategy 6 – Figure 1F). As in several other switch studies, clinical ratings were based on the use of PANSS, CGI, (modified) SAS, BAS, and AIMS. Regarding concomitant medication, it was allowed to pursuit stable premedication, but it should not be modified during the study period. In contrast, medications not allowed comprised SSRI, drugs that inhibit CYP2D6 or inhibit or act as a substrate for CYP3A4. Rescue benzodiazepine and antiparkinsonian drugs, at limited doses, were permitted for newly emergent symptoms. The 8-week trial was completed by 66% of the patients, but there were no significant drop-out rates both groups. However, interestingly, only 24% of the fast-switching group (group 1) but 34% of the slow-switching group (group 2) discontinued the study, with a slightly higher number of patients showing poor compliance in the latter group. The plateau strategy was justified by the hypothesis that due to its relatively long elimination half-life, a 7-to-10-day administration of ARI is necessary to develop full activity at the dopamine receptor before tapering of current antipsychotic treatment. With regard to efficacy and safety over the 56-day study period (baseline, days 7, 14, 28 and 56), there were no differences between the two tapering strategies, except that in the slow-tapering group, BAS scores were significantly higher after ARI medication. The high discontinuation rates are striking, especially in slow switching conditions (Table 2). This suggests that slow tapering does not offer any advantage. On the other hand, in both groups, ARI treatment led to significant decreases in prolactin, body weight, total cholesterol, triglycerides, but not in an increase of QTc or EPS. Plasma concentrations of ARI and its active metabolite dehydro-ARI were measured, but on days 14 and 56, the two groups did not differ in their ARI concentrations and no significant relation of drug plasma concentration to clinical efficacy was observed in these CYP2D6 genotyped patients.

Study 10 (Table 2): Finally, in a historical multicentre cohort 6-month study based on 3 different switching strategies by Obayashi et al. (2020), current treatment with other antipsychotics was continued in group 1 (strategy 6 – Figure 1F), called 'add-on' procedure by the authors, for at least one week after ARI was added. This investigation was carried out in real clinical practice conditions. Tapering off was immediately commenced in group 2 (strategy 3 – Figure 1C). In group 3, subjected to the hybrid strategy 5 (Figure 1E), pre-treatment was immediately discontinued ('direct switching'). ARI was immediately introduced in groups 2

and 3. In all 3 groups, the dosing of ARI was flexible during the 6-month treatment period. Monotherapy with ARI was achieved after a 55-day and 28-day median tapering-off duration in the add-on mode (group 1) and cross switching mode (group 2), respectively. The clinical state of the patients was assessed with the CGI-S, and the social adjustment was recorded, as well as adverse reactions. Most data were collected 6 months after the switch. 53.4%, 28.9% and 41.9% of the patients were submitted to direct switch, add-on switch or cross switch, respectively, who discontinued ARI treatment after 6 months. There were indeed numerous patients who presented exacerbation of psychiatric symptoms, which led to an interruption of the ARI medication in 14.6% of the subjects within 63 days (median value) (precisely: 12.7%: direct switching; 15.6%: add-on switching; 16.1%: cross switching patients). Among other reasons for stopping medication were adverse effects, mainly due to EPS. This adverse effect preferentially appeared in the add-on switch group. This resulted in an interruption of ARI administration within an average time period of 21.5 days: 11.3%: direct switching; 13.3%: add-on switching; 12.9%: cross switching of patients. At 6 months, survival proportions under ARI monotherapy were significantly higher in patients of the non-direct switching group (63.6%) (which comprises the add-on switching (71.1%) and cross switching (58.1%) groups) than in the direct switching group (46.4%). This study suggests that the administration of ARI as drug B is relatively safe and effective, but survival rates tend to be superior with add-on switching.

Switch studies on BREX

There are 4 reports on switching to BREX (Correll et al., 2019; Ichinose et al., 2021; Ishigooka et al., 2020; 2021) (Table 3). The consequences of cross-tapering switch (Strategy 3 – Figure 1C) were examined in two reports (Correll et al., 2019; Ichinose et al., 2021), but in one of these reports 4 different tapering off periods were described for drug A (Correll et al., 2019). Other authors used the variant plateau switch of strategy 3 (Figure 1F) (Ichinose et al., 2021; Ishigooka et al., 2020; 2021). It must be mentioned that two of these studies by Ishigooka and colleagues (Ishigooka et al., 2020; 2021) are based on one previous (original) study (Ishigooka et al., 2018). In one of the substudies (Ishigooka et al., 2021), there were only patients ($n = 186$) pre-treated with atypical antipsychotics (drugs A). They were also participants in the other substudy (Ishigooka et al., 2020) with 200 participants pre-treated with typical ($n = 14$) or atypical ($n = 186$) antipsychotics (drugs A), but different parameters were examined (confirmed by a personal communication, Kazunari Niidome, Otsuka, Japan).

Study 11 (Table 3): In the investigation with 4 groups of subjects affected by schizophrenia (Correll et al., 2019), their treatment was first switched from a current treatment with antipsychotics to a monotherapy with BREX in an open label conversion phase during 1 – 4 weeks, followed by a single-blind 4 – 7 weeks continuation phase (stabilisation phase) with the same antipsychotic agent (Correll et al., 2019). It is actually a posthoc analysis of data collected in a maintenance study (Fleischhacker et al., 2017). At the baseline visit and last visit of the conversion phase and at every 2 weeks during the stabilisation phase, the clinical situation of the patients was assessed with the PANSS and the CGI-S scale, and TEAE were also recorded. Among the prohibited comedications, there were all psychotropic agents, including antidepressants, olanzapine-fluoxetine comedication, mood stabilisers, benzodiazepines (except lorazepam or oxazepam (clonazepam, diazepam, if not available)) used as rescue medications), ramelteon and other non-benzodiazepine sleep aids (except zolpidem, zaleplon, zopiclone, eszopiclone for the treatment of insomnia)). Patients were included who had experienced an acute exacerbation of psychotic symptoms at screening (PANSS score > 80). Numerous antipsychotics were used as previous antipsychotic medication: risperidone (33.9%) > olanzapine (19.1%) > quetiapine (18.1%) > haloperidol (13.9%) > ARI (10.9%), and others. During the conversion phase, patients were converted to 1 mg/day BREX, a dose which could be adapted to 1–4 mg/day according to the clinicians' choice. The medication with other antipsychotics, if any, was gradually decreased using a variable schedule. The groups were defined by the length of time spent in this conversion phase, i.e. group 1: 1–7 days ($n = 17$); group 2: 8–14 days ($n = 42$); group 3: 15–21 days ($n = 54$); group 4: 22–33 days ($n = 291$). 404 patients entered in the conversion phase and 292 BREX-treated patients completed the 8-week study period. The relatively low number of patients in groups 1–3 prompted the authors to limit the statistical evaluation. The main reasons for discontinuation of the treatment in the 27.3% of patients who did not complete the 8-week study were withdrawal of the patient consent or the sponsor's decision to terminate the study early as a consequence of positive results of the interim analysis. PANSS and CGI-S scores decreased in all conversion groups as observed in stabilisation week 4, but apparently, at weeks 6 and 8, there were no further decreases. Moreover, there were no statistically significant differences between the conversion groups regarding these scores. In the group of patients undergoing a conversion period of 22 – 33 days the incidence of adverse effects was apparently lower than in the other groups over the 8-week treatment period. In particular, the frequency of the most frequent adverse effect, insomnia, was lowest in group 4 (11.5%). Clearly, it would have been interesting to get a more comprehensive picture of the switching strategy used in the patients, but this study suggests that a switching period of 22–33 days is an advantageous procedure.

Study 12 (Table 3): The main aim of a small open 8-week study conducted by Ichinose et al. (2021) was to evaluate the efficiency of BREX regarding improvement of side effects in 37 patients currently treated with other antipsychotics. Clinical symptom severity was evaluated with the instruments PANSS, CGI, and the DIEPSS, at baseline and endpoint. Benzodiazepines and anticholinergics were permitted. The switching strategy was not fixed but decided by the physician using clinical and biological criteria. Add-on switching (plateau-switch (strategy 6 – Figure 1F)) and cross-titration (strategy 3 – Figure 1C) was done in 64.9% and 35.1% of the patients, respectively. The patients were then separated into a dropout group ($n = 10$) and a completion group ($n = 27$): the discontinuation rate therefore reached 27%, but no comparison was presented with regard to the individual influence of the switching strategies on the clinical outcome. Apparently, belonging to either group did not depend on the switching strategy. At endpoint, the final BREX dose reached 1.9 ± 0.3 mg/day. The main advantages of switching to BREX were the improvement in EPS and metabolic side effects (body weight, BMI, HDL) and the significant decrease in prolactin concentrations, but it did not result in an improvement of efficacy as measured by PANSS.

The two following studies by (Ishigooka et al., 2020; 2021)) (study 13) and Ishigooka et al. (2021) (study 14) are post hoc analyses from data collected in an earlier longterm (52 weeks) investigation on the clinical effectiveness of a long term administration of BREX in 282 patients mainly included for requiring chronic antipsychotic treatment (Ishigooka et al., 2018). Subjects of the first analysis were pre-treated with typical or atypical antipsychotics (except clozapine) ($n = 200$) (Ishigooka et al., 2020),

while in the other analysis (Ishigooka et al., 2021), only subjects pre-treated with atypical antipsychotics were included ($n = 186$)

Study 13 (Table 3): In the 8-week study with 200 subjects presenting with schizophrenia, there was a 4-week switching phase from different antipsychotics to BREX (1 mg/day, increased to 2 mg/day by the end of week 4), followed by a 4-week post-switch phase (Ishigooka et al., 2020). The plateau strategy (strategy 6 – Figure 1F) was characterised by a gradual decrease of current antipsychotics during weeks 3 and 4 until complete discontinuation. As the BREX dose could then be adapted to 1- 4 mg/day after week 4, there was wide dose variability at the end of the study period: 1 mg/day: 1.8% of the patients; 2 mg/day 23.2%; 3 mg/day: 25%; 4 mg/day: 50%. Clinical ratings were performed with PANSS and TEAE for efficacy, and adverse effects were recorded with AIMS, BAS, and the Columbia Suicide Severity Rating Scale. Antiparkinson drugs were allowed as comedication. The 17% discontinuation rate was due to withdrawal of consent (9.5%), adverse effects (5.5%), and physician's decision (2.0%). This rate reached only 4.9% in patients in whom the previous antipsychotic treatment was carried out with ARI, in contrast to 25.4% in patients under pre-treatment with other antipsychotics. Reportedly, the most frequent adverse effects were nasopharyngitis (13.5%), schizophrenia (9.0%), insomnia (6.5%), headache (5.5%), and akathisia (5.5%). On the other hand, whether ARI or another antipsychotic drug was used as drug A, no significant changes in the PANSS scores occurred between baseline and week 8. Since 4 patients, including 3 patients pre-treated with olanzapine (approximately at the end of the switching period (!)), discontinued treatment because of serious adverse effects (schizophrenia ($n = 3$); akathisia ($n = 1$)), the authors suggest that the switching period should be longer than 4 weeks, especially when olanzapine is involved.

Study 14 (Table 3): As outlined above, the protocol of the other 8-week BREX study (Ishigooka et al., 2021) was rather similar and also based on the earlier study (Ishigooka et al., 2018). However, the 186 patients included were on current therapy with atypical antipsychotics before switching to BREX, and mainly biological parameters and adverse effects were examined. BREX doses were those already reported above (Ishigooka et al., 2020): 2 mg/day at the end of the 4-week switch-period, followed by 1–4 mg/day BREX during the 52 open-label period. Because of withdrawal of consent or adverse effects, 54.2% of the patients discontinued the study (32.9% patients treated with ARI administered as drug A; 54.8% with other antipsychotics). There were minimal changes during the 56-week study period, in total/LDL-/HDL-cholesterol, triglycerides, and glucose levels. There was a slight increase in mean body weight (ARI group: 1.1 kg; non-ARI: 0.4 kg), and in mean prolactin levels in the ARI group, while they decreased in the non-ARI group. Symptom severity scores as measured with the PANSS and CGI-S decreased similarly in both groups, but no statistical calculations were communicated. Treatment emergent adverse events occurred to a similar extent in both groups (86.6% vs 88.5%; serious: 9.8% vs 14.4%), but there was little change in EPS or in the QTc interval. The authors conclude that a switch to BREX results in a low long-term risk for metabolic abnormalities (including weight gain), hyperprolactinaemia, extrapyramidal symptoms and QTc changes. On the other hand, this study suggests that after the switch, a spectacular improvement in psychiatric symptoms is not to be expected. Due to their similar pharmacological profiles, it is not surprising that a switch from ARI to BREX, as expressed by the related rates of discontinuation, may be less risky than switching from other antipsychotics to BREX. The results also suggest that, at least in some patients, longer tapering periods may be advantageous in avoiding adverse effects.

CARI: Switch study

Study 15: Strictly speaking, there have hitherto been no published studies focused on the clinical efficacy, tolerability and safety of CARI after a switch from a current treatment with other antipsychotics to this PD2A in subjects affected by schizophrenia. Therefore, a 26-week study by Nemeth et al. (2017) will be cited here, the focus of which is on describing the switching procedure used in a pivotal investigation of a comparison of CARI with risperidone administered to schizophrenic individuals with predominantly negative symptoms, but without clinical precisions regarding the switching period. Clinical ratings were realised with PANSS, Calgary Depression scale for schizophrenia (CDSS) and SAS. Medication with additional psychotropic drugs were prohibited, except with some but not specified exceptions. In this 26-week double-blind treatment period, current antipsychotics were not changed during a 4-week lead-in period, but on day 0 (randomisation) a 2-week uptitration phase commenced, lasting until day 6, when the patients received 1.5 mg/day CARI (or 2 mg/day risperidone). Between days 7 and 13, the doses were 3 mg/day for both drugs. Finally, after day 13, the daily (target) doses were 4.5 mg/day and 4 mg/day, respectively. During this lead-in period, the other antipsychotics were tapered off and discontinued on day 14, but depending on the clinical situation, downtitration could be prolonged by 2 more weeks (cross-tapering switch: strategy 3 – Figure 1C). No information is available on the antipsychotics prescribed at inclusion, then tapered off and discontinued after randomisation. PANSS assessments were carried out 10 times, at baseline, at weeks 1, 2, 3, 4, 6 and later on, but statistical data were only communicated for those collected at week 26. It is of interest that 227 and 229 patients treated with CARI or risperidone, respectively, belonged to the modified intent-to-treat groups: 77% of patients in each group completed the 26-week treatment period. During the uptitration phase, 4% and 2% of the CARI and the risperidone groups discontinued respectively, while the corresponding figures are 19% and 21% for the continuation phase.

In the absence of studies targeting the switch period, some phase II/III trials are mentioned here that deal with introduction of a treatment with CARI in patients who initially underwent a 7-day washout period of previously administered antipsychotics. Some authors ((Durgam et al., 2016) proposed a flexible dose treatment initiated with 1.5 mg CARI on day 1, followed by an increase to 3 mg/day on day 2, and if necessary, to 4.5 mg/day on day 4, 6 mg/day on day 6, the maximum dose, and finally to 9 mg/day on day 10 (i.e. in off-label conditions), but no information is available on the pre-treatment of patients with antipsychotics. A similar design, initiated by slow uptitration with 1.5 mg CARI on the first day of treatment, was also used by the same group of authors in other studies (Durgam et al., 2014; 2015; 2016).

Discussion

This review compares studies in which different switch strategies were used for the replacement of a current antipsychotic treatment with the P2DA antipsychotic agents ARI, BREX or CARI with the aim of proposing the most promising clinical procedure in terms of clinical efficacy, safety and tolerability. The purpose was also to reveal possible differences between the three compounds with regard to an optimal switch strategy. However, the analysis shows that the available studies are very heterogeneous and difficult to compare. Indeed, the methodologies differ widely between the studies as to previous antipsychotic medication, doses of drug B used and study duration. Moreover, there are no

double-blind placebo-controlled studies which merit scoring as level A evidence (Bandelow et al., 2008).

The ARI studies were examined for group x time interaction effects regarding clinical efficacy of a switch. Several studies report that switching strategies led to a clinical improvement compared to baseline, at least in some parameters (PANSS, CGI-S or similar instruments) (Casey et al., 2003; Hwang et al., 2015; Kim et al., 2009; Pae et al., 2009; Ryckmans et al., 2009), but this was not observed (Chen et al., 2012; Takeuchi et al., 2008) or evaluated by other groups of authors (Lin et al., 2009; Stroup et al., 2011). In studies designed to compare patients the current antipsychotic treatment of whom was replaced by ARI with those who continued current treatment, no clear-cut differences in clinical efficacy (PANSS, CGI-S) were observed between switchers and non-switchers (Kim et al., 2009; Stroup et al., 2011).

Generally, no differences in clinical outcome were observed between the treatment arms with ARI (Casey et al., 2003; Chen et al., 2012; Hwang et al., 2015; Kim et al., 2009; Pae et al., 2009; Ryckmans et al., 2009). Casey et al., 2003 conclude that any of the 3 strategies used in their study can safely be applied in patients switched to ARI. This includes abrupt switch (strategy 1 – Figure 1A), which was examined in only one other investigation, but as the hybrid strategy 5 (Figure 1E), in that discontinuation of medication A occurred abruptly, while ARI was introduced at flexible doses (Obayashi et al., 2020). However, it is not clear whether in some patients a full ARI dose was immediately given, while in others it was slowly uptitrated. This makes a direct comparison between the Casey et al. (2003) 8-week study and the Obayashi et al. 6-month study (Obayashi et al., 2020) difficult, but the latter authors conclude that direct switching is less favourable due to an increased risk of patient withdrawal. Indeed, in another study an increase of clinical symptoms was observed in ARI patients one week after an abrupt switch from the previous treatment (Pae et al., 2009).

Adverse effects experienced during pre-treatment with various antipsychotics will depend on their pharmacodynamic profile, and therefore it is necessary to take account of the previous antipsychotic medication to interpret variations of adverse effects observed after introduction of ARI, but again, also pertinent here, data on the individual previous antipsychotic medication are rarely available from the studies. An example is the study (Casey et al., 2003), where most patients were previously medicated with olanzapine ($n = 55$), risperidone ($n = 37$) or haloperidol ($n = 8$) and in which a decrease in some adverse effects (weight, prolactin, QTc interval) and no deterioration regarding EPS were observed, but no data are available from subgroups of patients sharing the same previous antipsychotic medication. In another study, where risperidone and olanzapine were again the most often prescribed previous antipsychotics, the incidence of adverse effects was again not calculated according to the individual previous antipsychotic medication or the switch procedure (Takeuchi et al., 2008). The authors only reported that after the switch to ARI there was a decrease in body weight, total cholesterol, triglyceride and prolactin levels and QTc interval.

Cross-tapering switch (strategy 3 – Figure 1C) was the most frequently tested procedure (Chen et al., 2012; Kim et al., 2009; Obayashi et al., 2020; Pae et al., 2009; Ryckmans et al., 2009; Takeuchi et al., 2008) in studies about ARI used as drug B. Most authors conclude that a cross-tapering switch (strategy 3 – Figure 1C), can be successful regarding efficacy, safety and tolerability. There was a wide variability in discontinuation rates – between 3.5% and 41.9% depending on the studies. These rates appear not to be strongly dependent on the study duration (between 8 weeks and 6 months). In the study with particularly low discontinuation rates (3.5% and 5%) after the use of two switch procedures (strategy 3 – Figure 1C) and hybrid strategy 4 (Figure 1D), it is striking that only risperidone was given as a pre-treatment (Ryckmans et al., 2009). Both strategies led to a significant but similar clinical improvement as measured with PANSS and CGI-I scales in this open-label study. In other strategy 3 studies, risperidone and olanzapine were the most frequently administered antipsychotics before switching. However, it is difficult to evaluate their individual influence on patient outcomes, as no precisions were provided in most reports (Casey et al., 2003; Chen et al., 2012; Hwang et al., 2015; Lin et al., 2009; Obayashi et al., 2020; Pae et al., 2009; Stroup et al., 2011; Takeuchi et al., 2008). It is therefore noteworthy that in the study of Kim et al. (2009), no differences were found between subgroups of patients pre-treated with either risperidone or olanzapine, in time to failure to maintain remission, time to discontinuation of treatment for any cause or time to symptom worsening. None of the studies contains a clear warning regarding use of a particular strategy (hybrid strategy, plateau switch), but some authors (Obayashi et al., 2020; Pae et al., 2009) conclude that tapering off drug A instead of abrupt switching may be advantageous. Interestingly, higher discontinuation rates occurred more frequently under slow switching conditions (4 weeks) rather than under fast switching conditions (1 week) (Hwang et al., 2015), but the authors did not observe significant differences in terms of improvements in clinical symptoms or in the metabolic profile.

Among the few studies with BREX as drug B, that of Correll et al. (2019) suggests that a cross-tapering period of 22–33 days (strategy 3 – Figure 1C) is advantageous in that adverse effects over 8 weeks are less frequent than in shorter conversion periods, but that clinical efficacy is not enhanced. In the study of Ichinose et al. (2021), cross-tapering switch (strategy 3 – Figure 1C) and plateau switch (strategy 6 – Figure 1F) strategies were examined, but their effectiveness was not compared. Comparisons were only made between completers and drop-outs. Of particular interest are the twin studies on switching to BREX (Ishigooka et al., 2020; 2021), in which a subgroup of patients was subjected to a switch from one P2DA to another, namely from ARI to the P2DA BREX. However, all patients who participated in these investigations were only subjected to a plateau switch (Strategy 6 – Figure 1F). These studies suggest that the switch from ARI to BREX is accompanied by a lower discontinuation rate than a switch from other antipsychotics, but the percentage of adverse effects does not differ between these groups (Ishigooka et al., 2021), except that in patients previously treated with ARI, a slight increase of prolactin was observed after its replacement by BREX, whereas it decreased slightly in the other patients. There are only BREX switch studies based on the cross-tapering strategy 3 (Figure 1C) or the plateau switch strategy 6 (Figure 1F). It would certainly be interesting to collect information on the outcome of patients submitted to an immediate switch (abrupt discontinuation followed by full dose of BREX (strategy 1 – Figure 1A) from ARI to BREX or CARI to BREX, as they share similar pharmacological and pharmacokinetic properties.

Nevertheless, based on these BREX studies no evidence-based recommendation can be formulated for a particular switch strategy, except that in situations where drug A is an antipsychotic drug other than ARI, the authors (Ishigooka et al., 2020) suggest a switch period of several weeks. In line with recommendations formulated by these and other authors (Stahl & Stahl, 2020; Lin et al., 2009; Taylor et al. 2022), and also by the authors of this review, a prolonged switch period is especially recommended in patients pre-treated with anticholinergic antipsychotics such as olanzapine, clozapine or quetiapine.

As outlined above, only one study deals with a switch from antipsychotics to CARI, using a cross-titrating strategy (Strategy 3 – Figure 1C), but no data were communicated describing the efficacy, safety and tolerability of the drugs during the switch period (Nemeth et al., 2017). Some case reports describe switching to CARI, but they will not be considered here (Rancans et al., 2021). Clearly, such studies should be realised with groups of patients in order to create evidence-based data that will support recommendation of an optimal switch strategy.

Several national groups of psychiatrists have published recommendations about switching from antipsychotics other than PD2A to ARI (Fagiolini et al., 2015; Fraguas et al., 2022; Veznedaroglu et al., 2018). Experts from Turkey published recommendations for switching an antipsychotic treatment to ARI. They are mainly based on a carefully elaborated consensus rather than on a thorough presentation of the studies that could support their decisions (Veznedaroglu et al., 2018). The proposed switching strategies vary according to the clinical situation of the patients. In the three situations depicted (outpatients with stable schizophrenia, outpatients with recurrent psychotic exacerbation, switching in inpatients), plateau switches are recommended, but a full dose of ARI is only suggested in an extreme clinical situation such as exacerbation of the psychotic state while the patient is still at full dose of the previous antipsychotic medication. In contrast, Spanish experts preferentially recommend the cross-titrating switch strategy when ARI is intended to be introduced in patients pre-treated with other antipsychotics, but the experimental data on which this recommendation is based are not presented (Fraguas et al., 2022).

An international panel (Fagiolini et al. 2020) published recommendations for the switch from non-D2-receptor agonistic antipsychotics to CARI and discussed different approaches. One of these is based on the type of previous antipsychotic medication, with a special emphasis on pronounced antihistaminergic/antimuscarinic effects of antipsychotics such as olanzapine, quetiapine, and clozapine: a longer switching time is recommended. The latest case series utilised cross-titration and no tapering strategy when switching from clozapine to CARI, with improvement of the symptom complex (Duque-Yemail & Avila, 2022), reflecting growing clinical experience in this area. Furthermore, the role of pharmacokinetics and dynamics of antipsychotic drugs should be given special consideration when planning switching regimes (Keks et al., 2019).

Most reviews on switching strategies used for antipsychotics have in common that, as in the present review, each switch study was analysed separately, and meta-analyses or similar evaluations were infrequent (Buckley & Correll, 2008; Edlinger et al., 2005; Hatta et al., 2018; Newcomer et al., 2013; Weiden, 2006). This may be explained by the considerable methodological disparities between the different individual studies and the lack of data in the reports supporting such a project.

One group of authors (Takeuchi et al., 2017a; 2017b; 2018; Takeuchi & Remington, 2020) carried out systematic reviews and meta-analyses of studies looking at the clinical consequences of a switch from antipsychotics to other antipsychotics, mainly in subjects suffering from schizophrenia spectrum disorders. They included studies about all types of antipsychotics including ARI, but none of them dealt with BREX or CARI as drug B. In one of these meta-analyses, the authors (Takeuchi & Remington, 2020) concluded that wait-and-gradual antipsychotic discontinuation (this corresponds to a plateau switch (strategy 6 – Figure 1F) should preferentially be carried out when a cautious switch is needed. However, among the 6 studies included, only one deals with ARI as drug B (Pae et al., 2009). In another meta-analysis of 9 studies including 12 different switch strategies (Takeuchi et al., 2017a), they concluded that either immediate or gradual discontinuation of treatment with drug A may be advantageous, but only 2 studies present data on a switch to ARI (Casey et al., 2003; Pae et al., 2009). Another meta-analysis concerned 5 studies (only one study dealt with ARI, which compared gradual versus wait-and-gradual discontinuation: The strategies did not show differences in any clinical outcome (Takeuchi et al., 2017b). Finally, another meta-analysis led to the conclusion that a rapid initiation constitutes an option to be preferred in the treatment of acute schizophrenia, whereas slow initiation should be considered in stable schizophrenia (Takeuchi et al., 2018). However, the low quality of evidence should prompt further studies, especially since none of the acute schizophrenia studies included ARI-treated patients, while only two studies included stable schizophrenia subjects (Casey et al., 2003; Ryckmans et al., 2009). It is striking that these meta-analyses of Takeuchi et al. (Takeuchi et al., 2017a; 2017b; 2018; Takeuchi & Remington, 2020) were centred on the discontinuation strategies for drug A, since the role of handling drug B, either immediate introduction at full dose or stepwise titration, was rather neglected. As in the present study, they considered discontinuation rates as an important evaluation parameter, but also included in their meta-analyses the recorded scores of the clinical rating scales, such as PANSS, BPRS and CGI-S. If the data needed for the meta-analysis were not published in the reports, they contacted corresponding authors and/or funding pharmaceutical companies. These steps were not realised in the present study, and this may be considered as a limitation of the present review.

Conclusion

This analysis did not reveal evidence for a preferable switching strategy but highlighted that the most used switch strategy was represented by cross-tapering for the P2DA. There are numerous studies of the clinical efficacy, safety and tolerability of ARI after a switch from previous medication with various antipsychotics in individuals with schizophrenia spectrum disorders. RCT investigations are scarce with regard to BREX and, strictly speaking, absent with CARI. However, as clinical practice with these new agents advances, evidence regarding switch outcomes is urgently needed. Currently, the data collected are most often from open-label studies, none of which merits evidence level A. Whether optimal switch strategies differ between the three P2DA also remains an open question.

Restricted to clinical use, the present FDA and EMA recommendation for PD2A are a potential guide for clinical practice, but this approach does not provide any significantly higher level of evidence than the other for the switching strategies discussed in this paper. Consultation of the so-called online platforms, e.g. antipsychotic switching tool (https://www.nps.org.au/australian-prescriber/articles/antipsychotic-switching-tool (accessed on 1 December 2022)) can aid in clinical decision-making, but does not answer the original question about the evidence of switch strategies from non-agonistic antipsychotics to PD2A. To summarise, no clear evidence-based recommendations for different switch strategies is currently available.

This situation is further complicated by the considerable heterogeneity of the protocols of the available studies, thus hampering comparisons. This is in line with a statement already published over 10 years ago that large RCT are needed to answer the question about the best switching strategy and switching procedure (Hasan et al., 2012). It would be valuable to define a

protocol for future switch studies that defines, among other parameters and tools, the optimal duration of such investigations, the clinical and biological instruments to be used and the timing of the exams.

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ORCID

Pierre Baumann http://orcid.org/0000-0002-6253-5225
Philipp Bauknecht http://orcid.org/0000-0003-0423-8158
Maxim Kuzin http://orcid.org/0000-0002-0243-8458
Georgios Schoretsanitis http://orcid.org/0000-0002-3851-4117

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