

Exploring Hidden Issues in the Use of Antipsychotic Polypharmacy in the Treatment of Schizophrenia

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The mainstay of schizophrenia treatment is pharmacological therapy using various antipsychotics including first- and second-generation antipsychotics which have different pharmacokinetic and pharmacodynamic property leading to differential presentation of adverse events (AEs) and treatment effects such as negative symptoms, cognitive symptoms and comorbid symptoms. Major treatment guidelines suggest the use of antipsychotic monotherapy (APM) as a gold standard in the treatment of schizophrenia. However, the effects of APM is inadequate and less potent to achieve symptom remission as well as functional recovery in real practice which has been consistently reported in numerous controlled clinical trials, large practical trials, independent small studies and systematic reviews till today. Therefore antipsychotic polypharmacy (APP) regardless of the class of antipsychotics has been also commonly utilized for many reasons in real world practice. However, APP has also crucial pitfalls including increase of total psychotics including antipsychotics, high-doses of antipsychotics used, poor compliance, drug-drug interaction and risks for developing AEs, all of which are paradoxically related to poor clinical outcomes, whereas APP has also substantial advantages in reduction of re-hospitalization, severe psychopathology and targeted control of concurrent symptoms. Given currently limited therapeutic options, it is also important to properly utilize APP in order to maximize its clinical utility and minimize its risk for better treatment outcomes for patients with schizophrenia, based on risk/benefit with full understanding of pharmacological and clinical issues on APP. The present paper intends to address intriguing and important issues in the use of APP in real world practice.

KEY WORDS: Antipsychotics; Schizophrenia; Polypharmacy; Issue.

INTRODUCTION

Schizophrenia is a chronic disabling mental illness requiring enormous endeavor of medical professionals, family and public supports and costs since it is not easily cured and needs a long-term care due to its fluctuating and deteriorating clinical course over time [1]. The mainstay of the treatment for schizophrenia has been needless

to say pharmacological agents including antipsychotics. Indeed, the development and introduction of second-generation antipsychotics possessing differential pharmacodynamic (PD) property in comparison with the earlier, first-generation antipsychotics have significantly improved the biological treatment options in routine practice, providing better tolerability and safety which are substantially and critically involved in medication compliance and persistence [2].

However, the efficacy of antipsychotic therapy is not satisfactory in real world by which many next treatment strategies have been utilized in routine practice for offering better treatment outcomes for patients with schizophrenia, although some second treatment options such as antipsychotic polypharmacy (APP) are not officially rec-

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ommended by major treatment guidelines or fully supported by evidence-based data from randomized controlled, clinical trials (RCTs), cohort study and adequately-powered, well-designed practical trials [3-10].

Despite antipsychotic monotherapy (APM) is the gold-standard therapy recommended by well-known treatment guidelines from many popular and influential academic societies, APP has been also widely used for some proportion of patients with schizophrenia, for instance APP is commonly utilized and considered for treating difficult-to-treat cases or intolerance/failure to initial APM in naturalistic treatment settings [8,11-13]. In fact, the prevalence of APP showed quite wide ranges due to differences in methodological approach and samples included in such studies. The global median rate of APP was reported approximately 20% in a recent systematic review involving 147 studies [14], although there have been substantial variations among geographic regions [2,15-17].

Why do clinicians utilize APP for treatment of their patients with schizophrenia? Many persuasive reasons were reported in numerous studies where further control of psychotic symptoms especially positive symptoms ranked as the most important reason. Enhancement of cognitive impairment, decrease of readmission, prevention of relapse/recurrence, avoidance of high-dose AP therapy, overlap for AP switch, target treatment for specific and/or comorbid symptoms including anxiety, sleep disturbance, depression, violence, and agitation, counteract adverse events (AEs) using differential PD profile [18-22]. However, APP has also clear disadvantages including diverse AEs such sedation, increased rate of metabolic syndrome, somnolence, reduced concentration and extrapyramidal symptoms (EPSs), complexity of treatment regimen, drug-drug interaction, high medical costs, unclear determination on treatment response among APs, poor compliance/persistence to treatment, and increased total doses of APs [20,23-25].

Apart from debate on whether APP is necessary or excessive treatment approach beyond major treatment guidelines recommended by academic or regulatory authorities and/or it is adequately supported by sufficient evidence from large RCTs, APP has already positioned as one of routine practices. If so, it should be wise and realistic to discuss about hidden points in the use of APP for real world practice. Thus, the present paper elucidates some intriguing and practical points considered in the uti-

lization of APP in routine practice.

WHEN AND HOW TO INITIATE APP?

Most treatment guidelines state that APM should be the first-line treatment and APP should be a treatment strategy of last resort for treatment-resistant schizophrenia [2-10]. They stated that clozapine should be tried in the first place to overcome inadequate treatment response from different APM trials. At least two or more APM failures lasting for more than 4-month for each APM are usually required for proceeding to next treatment options [9].

Addition of another AP to clozapine should be an easy next step when patients have already shown a partial response. Indeed, many studies have shown beneficial effects of APP combining clozapine and another AP. According to a meta-analysis [26] investigating 4 RCTs, addition of another AP to preexisting clozapine was found to be beneficial to cases with adequately-tested prior APM for at least 4–6 weeks, indicating a premise (adequate duration of prior APM) should be mandatory to achieve optimal clinical outcomes.

Such findings were also replicated in the subsequent meta-analysis [27,28] and independent studies [29,30]. APP can be started in specific clinical situations in reality as follows: a failure to at least two or more APM, a failure to clozapine, partial response to clozapine, intolerance to APM including clozapine, clozapine-contraindicated case, counteract AEs from initial or another AP in APP regimen.

As for doses of individual AP in the use of APP, there has been no well-evidenced data to support whether clinicians should escalate the dose of later AP up to maximal therapeutic dose to achieve treatment response as targeted in combination with initial existing AP. When reflecting one of the advantages of APP is to prevent excessive use of high-dose APM leading to serious AEs or poor compliance, minimal but effective dose of later AP (compatible with D₂ occupancy of 65%) should be optimal along with regular assessment using measurement-based evaluation on patients' psychotic symptoms, which will definitely protect patients from unnecessary sufferings which can be potentially caused by overdoses of APs.

TOTAL NUMBER OF APP OR TOTAL DAILY DOSE OF APP, WHICH IS MORE PROBLEMATIC?

APP results in an increased number of daily pills leading to high-dose AP therapy in routine practice. The total AP dose of APP is especially problematic when combining APs with high D₂ receptor affinity and blocking effects for treating patients since it will cause cumulative impacts on the appearance of unwanted side effects (SEs) such as EPS [12]. Significant relationship has been consistently between antipsychotic effect (including SEs) and degree of D₂ receptor occupancy [31].

In fact, patients with EPS had significantly higher D₂-receptor occupancy than those without, indicating the harmful effects of total dose on the development of EPS. Overall APs are known to show balanced efficacy with D₂ occupancy of 65%, while the development of SEs such as hyperprolactinemia and EPS may increase when D₂ receptor occupancy exceeds 72%, and 78%, respectively, although inter-individual differences exist in D₂ receptor occupancy [31,32].

In addition, D₂ occupancy levels were significantly related with the vigilance and the summary scores in the measure of neurocognitive functions in the largest practical clinical trial, the Clinical Antipsychotic Trials in Intervention Effectiveness (CATIE) trial [33]. The results clearly demonstrated a nonlinear relationship between prescribed AP doses and overall neurocognitive function and vigilance; they were especially impaired in subjects who showed D₂ receptor occupancy level approximately, of > 80%. Therefore, we may confirm that D₂ occupancy of > 80% not only increases the risk for EPSs as consistently reported in the literature but also increases the risk for cognitive impairment [33]. These are in line with the results from other APP studies that demonstrated the total dose effects of AP in association with cognitive dysfunctions between APP and APM [34,35], favoring APM over APP.

Likewise, it was also found that AP total dose also mediates the association between polypharmacy and QTc interval [36]. In the study, the Baron and Kenny mediational approach with adjustment for confounding variables demonstrated that APP was significantly associated with QTc prolongation, APP was also significantly related with AP dose, AP dose was also significantly associated with

QTc prolongation, however, APP was no longer associated with QTc prolongation under control of AP dose, which clearly indicate the crucial determinant of QTc prolongation was the AP dose but not number of APs in APP [36].

An interesting recent Swedish cohort study with the first-episode schizophrenia found that excess and overall cardiovascular mortality in schizophrenia could be influenced by other underlying biological and clinical factors rather than AP treatment when used in adequate dosages [37]. According to the results, small to moderate AP dosage uses were associated with substantially lower mortality than high dose AP usage where a high dose AP usage was in particular significantly associated with a higher mortality in female than in male patients. The subsequent study also clearly replicated the critical impact of inappropriate use with high dose of APs on overall mortality in schizophrenia patients [38].

IS INSIGHT ONE OF ISSUES IN THE USE OF APP?

Poorer insight of schizophrenia patients was found to be significantly associated with more likelihood of receiving APP in admission in a Italian large study ($n = 1,022$) [39], while patients with APM presented good insight in the study. Despite such finding presenting a direct association between insight and APP, it should be weighed since insight is critically involved in many treatment issues in schizophrenia patients. Indeed, insight is one of crucial components determining medication persistence and adherence of schizophrenia patients, which is very important in the treatment of schizophrenia since AP maintenance therapy is the gold standard and principle in the treatment for schizophrenia and the negative relationship between insight and treatment adherence is consistently reported in schizophrenia patients [40,41].

The strong link between impaired insight and non-adherence to AP was also replicated in the CATIE trial [42]. In the study, patients were classified by three groups depending on their insight such as no impairment (Positive and Negative Syndrome Scale [PANSS] G12 = 1), minimal impairment (PANSS G12 = 2–3), and moderate-to-severe insight impairment (PANSS G12 \geq 4). According to the results, the adherence rates were 17%, 20%, and 25% of patients with no, minimal, and moderate-to-severe insight

impairment at month-6 after study initiation, and 31%, 37%, and 43% at month-18. The time to nonadherence was also significantly shorter in patients with moderate-to-severe insight impairment (13.5 months) than in patients with minimal (14.4 months) or no impairment (15.1 months) [42]. A prior longitudinal analysis of the CATIE data also showed a strong relationship between insight and development of positive attitudes toward AP treatment which is directly associated with substantial improvement of clinical outcomes including psychopathology, community functioning and greater medication compliance in schizophrenia patients [43]. Therefore, we reasonably assume the strong relationship between insight, adherence and APP in the treatment of schizophrenia.

IS THERE ANY BEST-AVAILABLE APP REGIMEN FOR TREATMENT OF SCHIZOPHRENIA?

There has been scarce data regarding whether one specific APP regimen should have a superiority over another APP regimen. Interestingly the longest and largest cohort study ($n = 62,250$) followed 20-year [24] has found that significantly lower psychiatric rehospitalization among all 29 different APM and APP types was found in clozapine plus aripiprazole APP, resulting in 14% to 23% lower risk of rehospitalization than clozapine APM. Furthermore such difference in psychiatric rehospitalization between clozapine plus aripiprazole APP and clozapine APM was more profound in first-episode patients favoring clozapine plus aripiprazole APP over clozapine APM (hazard ratio = 0.78 and 22% difference). Any APP presented a 7% to 13% lower risk of psychiatric rehospitalization compared with any APM, indicating that rational APP excluding clozapine plus aripiprazole could be also clinically useful treatment strategy regardless of combined APs as APP regimen, especially with the use of two different APs possessing different types of receptor profile (i.e., D_2 receptor antagonist + partial agonist; D_2 receptor tight binding agent + loose D_2 receptor binding agent).

HOW LONG SHOULD WE MAINTAIN APP IN ROUTINE PRACTICE?

A previous study evaluated the prescription trend of AP switch and APP use in the real-treatment settings from a

longitudinal perspective [44]. In the study, APM was started with 208 patients in which 34.1% of the patients left APM and switched to different APs (27.4%) and/or APM (17.8%) within 2 years. Intriguingly inadequate efficacy of AP was the main reason for AP switch, however, it was improperly conducted since the APM dose was below the recommended range in 47.4% of the AP switch and APP was also prematurely used after a median of one AP trial for only 3 months even in AP-naïve patients, indicating that clinicians might utilize AP switch and APP not based on treatment guidelines or consensus but possibly by empirical, preferential, and easy approach as a next treatment step.

In fact, there have been a dearth of data regarding how long APP can last for treatment of schizophrenia. Symptomatic remission has different criteria using psychometric assessment such as PANSS, the Scale for the assessment of negative symptoms and positive symptoms (SANS/SAPS), and the Brief Psychiatric Rating Scale (BPRS) [45]. It can be evaluated with 8 items in the PANSS (delusions, unusual thought content, hallucinatory behavior, conceptual disorganization, mannerisms/posturing, blunted affect, passive/apathetic social withdrawal, and lack of spontaneity and flow of conversation), all of which have to be simultaneously scored with mild or less symptom severity (≤ 3 points). Use of BPRS (severity ≤ 3 points) criteria may be supplemented by use of the SANS (severity ≤ 2) points criteria for evaluating overall remission since it does not include assessment of negative symptoms [45,46]. The cut-off time for evaluation whether patients remitted from psychotic symptoms of schizophrenia are usually 6-month [45] by which we can assume that APP transition to APM should be ready or prepared around 6-month upon achieving symptomatic remission in a patient with schizophrenia; however, it should be properly determined based on a patient's current clinical situation since symptomatic remission can be achieved and maintained for a certain period and but functional recovery may not be sufficient yet. Indeed, many working groups [47-51] tested such time differences between symptomatic remission and functional recovery in patients with schizophrenia.

Indeed, a significant difference in functional capacity between remitters and nonremitters does not necessarily mean that remitters are functioning well. In addition, vocational/occupational status is possibly influenced by others

factors not depending on remission status [46]. Furthermore, it has been known that first- and multiple-episode schizophrenia may have differential chances of fulfillment of remission. According to Dr. Lambert and colleagues' [46] excellent review that analyzed more than 30 studies, they concluded that first-episode patients display higher remission frequencies during follow-up (48% vs. 43%) when comparing first- and multiple episode completers, using the severity and time remission criteria and there is an increase of remission frequencies between 6-month and 24-month follow-ups (6-month: 46%, 12-month: 52%, 24-month: 63%) when using the severity remission criteria only in both groups. These findings clearly point out that remission frequency could be different by episode of schizophrenia favoring first-episode over multiple episodes and also much longer time should be also considered as a cut-off time for the determination/assessment of remission status in practice.

In a small retrospective study, it was found that APP ranged from 6 months to surprisingly, greater than 9 years [52]. In a recent mental healthcare database study, the long-term APP for more 6-month use was 23.1% among 10,945 cases with 4.5 years' mean follow-up [53].

Therefore, it should be very difficult for clinicians to establish exact time for APP (using two APs) transition to APM or for discontinuation of AP(s) among multiple APs-used APP (more than 3 APs) based on currently available, limited evidence and numerous clinical factors involved with APP. Such duration issue of APP been also confronted in several APP trials using clozapine and another AP [26,27]. Hence it should be reasonable to say that when a patient remits from a full domain of psychotic symptoms and maintain clinical stability over 6 months, careful and gradual discontinuation of one AP among APP regimen (i.e., two APs) can be considered for switching to APM or for reduction of APP regimen (i.e., more than 3 APs) in accordance with clinical status of individual case. On the other hand, long-standing maintenance of APP can be also justifiable when relapse occurs upon switching to APM [8]. When reflecting a need of personalized treatment and highly diverse clinical course of schizophrenia case-by-case, it should be more pertinent that clinicians should ascertain the lowest effective AP dosages in the use of APP to optimally prevent both relapses and AEs, and to allow optimal functional recovery, rather than being troubled by determining wheth-

er to maintain or discontinue antipsychotics [13,54].

HOW TO SWITCH APP TO APM IN CLINICAL PRACTICE?

In some studies, APP stay or switch to APM were tested. According to the previous systematic review including one RCT and two open-label trials [55], in two of three studies, more than two thirds of the subjects successfully moved from APP to APM (40/58, 69.0%; 34/44, and 77.3%, respectively) indicating that switch from APP to APM may appear feasible in a majority of schizophrenia patients in routine practice. Essock *et al.* [56] has also tested the feasibility of switching to APM from APP in a 6-month randomized and naturalistic follow-up study where all-cause discontinuation rate and time were more frequent and shorter in switch to APM than in APP stay, however, two-thirds of patients succeeded in switch to APM without group difference in worsening of psychotic symptoms. To address knowledge gap on APP stay and switch to APM, another 12-week RCT compared two treatment strategies of APP stay and switch to APM [57]. Seventeen and eighteen patients who have been on APP with stabilized doses for each AP were randomly assigned to either APP stay (continuation of two APs) or switch to APM (discontinuation of later AP), respectively. The primary endpoint was the change of BPRS score from baseline to the end of treatment, where early drop-out related with clinical worsening occurred in 5.8% of patients with APP stay, while 22.2% of patients with switch to APM. However, there was no indication of clinical worsening with switch to APM as measured by BPRS and Clinical Global Impression-Severity scores. Approximately 80% (n = 14) of patients with APP was able to be safely switched to APM with no clinical deterioration, in which the risk for clinical worsening was prominent in the first few several months.

However, such successful switch to APM from APP was challenged in a 7 multi-center study by Constantine *et al.* [58]. One hundred and four (n = 104) stable outpatient schizophrenia on 2 APs were randomly assigned to stay on APP or to switch to APM, where patients switched to APM showed greater symptom worsening than patients with APP stay. Such differences were prominent in the second 6months of the study. All-cause discontinuation rates over the 1-year trial were also significantly higher in

the switch to APM group than in the APP stay group (42% vs. 13%).

More interestingly the risks and benefits of switching from APP with two non-clozapine oral APs and APP involving either clozapine or an injectable antipsychotic were investigated in a recent study [59]. In total, 90 psychotic patients were randomized to APP stay or to switch to APM. The assessment was performed every 2 months for one-year follow-up period. Switching group involving either clozapine or an injectable AP did not differ over time from APP stay group on either symptom control or SEs, while significantly more worsening of psychotic symptoms was found in switching group with two non-clozapine oral APs. This data suggests that APP involving clozapine or injectable APs may be easier and safer to be switched to APM rather than APP with two non-clozapine APs, possibly indicating differential risk of APP switch to APM depending on the regimen utilized.

In addition, according to the recent meta-analysis to find the predictors of successful AP dose reduction in schizophrenia including 37 trials [60], young age (≤ 40 years), short duration of illness (≤ 10 years), and low post-reduction chlorpromazine equivalent dose (CPZeq) (≤ 200 mg/d) were found to be significantly associated with risk of relapse. The relapse rate was significantly higher (risk ratio [RR] = 1.96) in the AP dose reduction group than the AP dose maintenance group, whereas neuro-cognition significantly more improved in AP dose reduction group than in AP dose maintenance group. Clinical deterioration was mostly re-stabilized by increasing the dose to the baseline level in 87.5% of the studies. Interestingly a subgroup analysis clearly indicated that only a post-reduction CPZeq dose ≤ 200 mg/d was associated with an increased risk of relapse by 2.79 of RR. This data clearly indicates the AP dose reduction should be possible but clinicians need to keep the dose in therapeutic range of individual AP, at least corresponding to CPZeq dose of 200 mg/d or more.

DISCUSSION

According to a survey study [61], clinicians preferring APP had more clinical experience, see more patients per week, and had their own specific APP regimen as well as being attending physicians rather than resident doctor, continuing APP of prior physicians (75% was inherent

from previous prescribers) and having little concerns on APP treatment strategy. However, there were no differences in justification and concerns in the use of APP. These data clearly suggest that most clinicians use APP under similar purpose for enhancement of treatment outcomes and with careful considerations for minimization of AEs regardless they prefer APP or not. Interestingly another survey has found that clinicians preferring APP shares similar concerns such as unexpected potential AEs of APP regardless they are heavy or light APP users ($< 30\%$ of patients) [62]. Indeed, the AEs of AP use have not been intensively and widely studied in routine practice, however, a recent systematic review [63] including 53 researches has shown critical points regarding AEs in the use of APPs, stating that APP with longer duration may be significantly associated with increased frequency and greater severity of AEs, although it should be more replicated in subsequent long-term comparative studies, especially with high-dose APM.

Different perspectives have already started to recognize APP as one of proper and feasible next treatment options in the treatment of schizophrenia in routine practice. Some experts proposed active inclusion of APP with pragmatic recommendations into practice guidelines for schizophrenia [8,64]. Obviously, data concerning superiority of APP over APM or other treatment options for treatment of schizophrenia is still scarce today, no high-quality RCTs have proven such crucial issues, however, some subgroup of schizophrenia definitely benefits from APP rather than APM.

Meanwhile many proportions of APP patients can be also safely switched to APM or just stay in APP retaining similar efficacy after stabilization, and some proportion of APP patients also continue same treatment approach in a longstanding period without tolerability issues, indicating a potential utility of APP as long-term maintenance treatment option for schizophrenia.

The largest and longest nationwide cohort study has clearly revealed that no single APs or APPs excluding clozapine plus aripiprazole combination should supersede the efficacy of clozapine alone in terms of psychiatric hospitalization, which clearly pointed out the beneficial effects of specific APP on predefined or confined treatment targets. The relatively weak D_2 antagonist properties of clozapine might be enhanced by aripiprazole, which provides greater affinity for D_2 receptors. This should be in

Table 1. Consideration points in the use of antipsychotic polypharmacy in routine practice

APP is common and effective treatment option in clinical practice regardless of diagnosis
Thorough review for past and family AP response before instating APP
Active engagement of patients in decision of APP application
Regular assessment for clinical status would be useful for initiating APP or returning to APM
Clozapine and aripiprazole appear the most beneficial APP combination based on clinical trial data
Closely monitor the total dose of APP to avoid unnecessary and serious adverse events or adverse reactions
Consider long-acting injectable antipsychotics when clinical status is stabilized and upon transition to APM
A failure to at least two or more APM, a failure to clozapine, partial response to clozapine, intolerance to APM including clozapine, clozapine-contra-indicated case, counteract AEs
Consider reinstating immediate prior APP regimen if symptom worsening emerges when reducing APP regimen
Keep the total dose of APs up to chlorpromazine equivalent dose of 200 mg/d regardless of classes of APs when tapering off APP regimen
Gradual tapering of AP should be always kept in mind upon transition to APM or reduction of APP regimen
When reflecting a need of personalized treatment and diverse clinical course of schizophrenia, clinicians should decide the lowest effective AP dosages in the use of APP
Strong relationship is found between insight, adherence and APP in the treatment of schizophrenia

APP, antipsychotic polypharmacy; AP, antipsychotic; APM, antipsychotic monotherapy; AEs, adverse events.

line with the fact that beneficial effects of APP may come from synergistic effects on differential PD profiles, although additional effects of different PK profile among APs combined might be also partly involved in such effects. Table 1 addresses some clinical points in the use of antipsychotic polypharmacy in routine practice [65-68].

Given mentioned, APP has never been far from our routine practice but it has been staying indeed popular for a long time in naturalistic treatment settings. Reflecting insufficient and limited treatment options for schizophrenia, pertinent, reasonable and well-targeted usage of APP based on currently available evidence should be more practical and realistic in the treatment of schizophrenia in routine clinical practice.

■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

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