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Antipsychotic Polypharmacy:

A Comprehensive Evaluation of Relevant Correlates of a Long-Standing Clinical Practice

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OVERVIEW

The treatment of schizophrenia has remained a challenge despite various pharmacologic advances.¹ Although antipsychotic treatment is the cornerstone of successful treatment of the acute psychotic episode and of relapse prevention, evidence-based therapies are currently still limited to the use of medications with antidopaminergic activity.² This restriction to antidopaminergic therapy is caused by absent knowledge about the exact pathophysiological mechanisms underlying the exacerbation, persistence, and relapse of psychosis, precluding the development and implementation of rational pharmacologic augmentation and combination strategies in the management of schizophrenia.

One common strategy for the management of refractory and significant residual psychotic signs and symptoms is the use of 2 or more antipsychotics, also called anti-psychotic polypharmacy (APP). In a separate article,³ we undertook a systematic literature review of APP prevalences across 4 decades and geographical regions. Pooling data from 147 studies published between the 1970s and 2009, we found a median APP prevalence of 19.6% (interquartile range [IQR] = 12.9%–35.0%). We also found significant differences in pooled APP prevalences across geographical regions, with higher prevalences observed in:

- Asia (median = 32%, IQR = 19.2%–53.0%) and
- Europe (median = 23%, IQR = 15.0%–42.1%)

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compared with:

- North America (median = 16%, IQR = 7.2%–24.4%) and
- Oceania (median = 16.4%, IQR = 9.8%–20.0)

Although in North America, global APP prevalences were lower than in Asia and Europe, the median APP prevalence in North America increased steadily from 12.7% in the 1980s to 17.0% in the 2000s. Conversely, the median APP prevalence in Asia markedly decreased monotonously from 55.5% in the 1980s to 19.2% in the 2000s, whereas in Europe an increase from the 1980s (17.6%) to the 1990s (26.3%) was observed, followed by a plateau in the 2000s (25.0%).³

Multiple reasons for the use of APP, considered both appropriate and inappropriate, have been discussed (Table 1).⁴ Justifiable reasons for antipsychotic combinations include active cross-titration and the co-utilization of a different route of administration. Theoretically justifiable reasons include the treatment of different symptom domains (such as cognitive and negative symptoms), or of comorbid conditions (such as anxiety, insomnia, depression); the exploitation of pharmacodynamic or pharmacokinetic drug-drug interactions hoping to augment or speed up the efficacy of the first antipsychotic, especially after insufficient response to clozapine; and the exploitation of pharmacodynamic or pharmacokinetic drug-drug interactions hoping to minimize adverse effects.^{5–9} Reasons, which are difficult to justify, include arrested cross-titration caused by intraswitch symptom improvements, miscommunication between services, reliance on unfounded marketing strategies, patients' or family's demand without supportive data for that given individual, and idiosyncratic prescriber habits.^{4,7,10}

Over the years, APP has even become a source of debate and strong concern.^{4,11–16} Several states have included the reduction of APP as a key performance improvement and quality-of-care target.¹⁷ This situation stems mainly from the fact that robust evidence is lacking for the effectiveness of APP.^{18,19} Moreover, although several potential reasons for APP have been discussed, significant concerns exist, fueled by the fact that most reasons are not justified or not backed up by data, and that there are potential downsides to combining antipsychotics (see Table 1).

Concerns include the possibility of higher than necessary total chlorpromazine equivalent dosages, increased acute or long-term side effects, anticipated (or unanticipated) drug-drug interactions, increased noncompliance caused by an increased complexity of drug regimens, difficulties in determining cause and effect of multiple treatments, and substantially higher cost.^{4,15,16,20–22}

Although even monotherapy with newer antipsychotics that block multiple receptor systems and subsystems at a lower dose than is required to lead to dopamine blockade that is sufficient for antipsychotic efficacy²³ can already be considered a type of intrinsic polytherapy, the use of antipsychotic cotreatment is generally discouraged by treatment algorithms and is suggested only as a last resort strategy after clozapine (the standard of care for treatment-refractory psychotic illness) has failed.^{24–29} Nevertheless, many patients receive APP in clinical practice,³ despite a general dearth of controlled data on the efficacy and safety of this strategy.^{18,19} Because of this critical gap between clinical practice and evidence-based data, APP was recently listed among the 10 areas in schizophrenia research that are in dire need of investigation.³⁰

Although debated, discouraged, and defamed, rationales and correlates of APP are unclear. Therefore, in order to provide leads for a better understanding of the motivation for using

more than 1 antipsychotic concurrently and to guide initiatives for a reduction of potentially inappropriate use of APP, we reviewed the literature regarding correlates of APP.

METHODS

We conducted an electronic search in PubMed for correlates of APP (last update September 09, 2011), using the following key words: “(antipsychotic OR antipsychotics OR neuroleptic OR neuroleptics) AND (polypharmacy OR combination OR combined OR comedication OR concomitant OR cotreatment OR adjunct OR adjunctive) AND (human) AND (schizophrenia OR schizoaffective OR psychosis OR psychotic OR bipolar OR mania).” In addition, reference lists from retrieved articles and relevant reviews were surveyed to identify additional studies.

Articles were included that reported explicitly on significant or nonsignificant associations between APP and study design, patient, illness, treatment, and prescriber characteristics. We excluded associations between APP and adverse effects, because this was the topic of a separate review, requiring a more fine-grained assessment of individual APP combinations, which can yield different outcomes, including opposing effects of increased or even decreased adverse effects with some combinations.³¹ Whenever multiple regression analyses were reported, these results, rather than results from univariate analyses, were included, in order to focus on independent associations whenever possible. Only results that were either explicitly significantly different or explicitly not significantly different between patients treated with APP or antipsychotic monotherapy were included in this review, using descriptive statistics.

RESULTS

Out of 6416 initial hits, 5996 articles were excluded on the abstract level, and 447 full text articles were reviewed. Of these articles, 98 studies provided explicit information on study patient, illness, treatment, prescriber, or study design associations with APP and are included in this review.

STUDY CHARACTERISTICS

The 98 included studies were published between 1977 and 2011, reported on 611,078 patients (range: 38–116,114; median: 534; IQR: 225–3047), and originated from Europe (N = 47, 48.0%), the United States and Canada (N = 37, 37.8%), Asia (N = 11, 11.2%) and Oceania (N = 3, 3.1%). Sixty-seven studies (68.4%) were cross-sectional and 31 (31.6%) were longitudinal. About half of the studies (N = 45, 51.1%) were conducted in inpatients, whereas the rest of the studies were conducted in outpatients (N = 24, 27.2%) or patients treated in both settings (N = 19, n = 21.6%). Among 60 studies that specified the time period of their assessment, most (N = 32, 53.3%) covered the time period between 2000 and 2010. The remaining studies covered the 1990s (N = 16, 26.7%), late 1990s into early 2000s (N = 6, 10.0%), 1980s (N = 3, 5.0%), 1970s (N = 2, 3.3%) or the period spanning the 1970s to 1990s (N = 1, 1.7%). Among 95 studies with information, 88 (92.6%) were conducted in adults and 7 (7.4%) were conducted in children and adolescents. Patients were on average 41.3 years old (66 studies with information), 58.7% were male (83 studies with information) and 60.3% were white (25 studies with information). In 68 studies with diagnostic information, 66.7% had a diagnosis of schizophrenia or schizophrenia spectrum disorders (range: 3%–100%, median 70.5%). APP was defined simply as the use of 2 or more antipsychotics at the study assessment time point in most studies (86, 87.8%). The remaining studies required a minimum duration of APP of at least 3 to 7 days (N = 4, 4.1%), 28 to 30 days (N = 2, 2.0%), 60 days (N = 4, 4.1%), or 90 days (N = 2, 2.0%). Across

studies reporting on APP correlates, the mean APP prevalence was 29.9% (range: 3%–95%; IQR: 14.6%–46.0%; median: 26.7%).

PATIENT CHARACTERISTICS

Substantial evidence exists for the association of younger age and APP (Table 2).^{5,32–41} Only 1 study found older age to be associated with APP,⁴² and 1 study reported that APP was more common in adolescents than in children.⁴³ Moreover, except for 1 study that found females to be treated with more APP,⁵ all other studies reported that male sex was associated with higher APP utilization. Data on race and ethnicity were inconclusive. Some studies reported higher APP in White/non-Latino patients,^{40,44} others showed either higher³⁸ or lower³⁶ APP prevalences in Blacks/African Americans, and 1 study reported no differences between Whites and Blacks.⁴⁵ By contrast, 4 studies reported that APP was more common in unmarried patients (see Table 2).^{5,36,44,46}

ILLNESS CHARACTERISTICS

APP was most prevalent in patients with schizophrenia and schizoaffective disorder and^{5,35,39,46–53} psychotic disorders (Table 3).^{32,43} Moreover, APP was more common in patients with earlier illness onset⁴⁷ and longer illness duration,^{54–60} with only 1 study finding the opposite.⁵ Furthermore, APP was consistently related to greater illness severity or acuity.^{5,7,36,40,47,53–55,61–65} Only risk of relapse was not increased in APP patients in 1 2-year study.⁴⁷ In addition, patients with APP showed less treatment improvement,²⁰ had less illness insight,^{46,47} greater treatment resistance,^{55,66} a history of violence,⁶⁰ and more negative symptoms.³⁵ The effect of comorbidities was assessed. Psychiatric comorbidity,³⁵ in general, and more comorbid depression³⁶ and nicotine use⁶⁷ were related to APP. Conversely, data on substance use were mixed, showing both higher^{40,63} and lower^{8,36} APP prevalences (see Table 3).

TREATMENT SETTING AND MEDICATION CHARACTERISTICS

Treatment setting variables associated with APP also point toward greater illness severity (Table 4). These variables include involuntary treatment,⁵² inpatient treatment,^{53,63,65,69–71} longer inpatient stay,^{60,69,72,73} except for 1 study,³³ and longer treatment in general.^{53,68} In addition, a history of multiple antipsychotic switches³⁸ and nonadherence or partial medication adherence^{74,75} was related to APP. Patients receiving APP at study baseline were also more likely to receive APP at end point in prospective studies (see Table 4).^{5,64,76}

One of the most consistent and replicated findings is the relationship between APP and greater total antipsychotic dose (see Table 4).^{18,36,37,48,50,52,56,71–73,77–95} In addition, treatment with quetiapine,^{20,38,50,68,73,96–98} depot antipsychotics,^{99–101} and first-generation antipsychotics (FGAs)^{68,78,85,102} has also been consistently associated with APP. Conversely, results regarding treatment with clozapine and olanzapine have been mixed. Some studies showed greater clozapine^{35,68} and olanzapine⁹⁶ utilization among APP users, whereas others showed lower clozapine¹⁰³ or olanzapine⁶⁸ prescribing. In a single study, APP was associated with less treatment discontinuation of aripiprazole.¹⁰⁴

Not surprisingly, because of the increased total antipsychotic dose, anticholinergic use was significantly higher in patients receiving APP than in those treated with anti-psychotic monotherapy.^{36,54,56,68,72,84,85,92,100,105–114} In addition, cotreatment with antidepressants,^{47,70} anxiolytics,^{47,54,70,79} and mood stabilizers^{36,68,79} has also been associated with APP (see Table 4).

PREScriBER CHARACTERISTICS

APP varied substantially by region and provider (Table 5).^{55,56,59,83,115–118} Higher APP use has been reported for metropolitan location/populations,³² nonteaching hospital settings and those with less research involvement.^{119,120} In addition, higher APP was associated with less physician attendance of local continuous medical education events,¹¹⁹ but greater attendance at educational programs sponsored by a pharmaceutical company.⁷⁰ Furthermore, APP has been associated with (see Table 5):

- Treatment by the same doctor for more than 2 years⁷⁰
- Treatment by a more senior staff member as opposed to a trainee¹⁰
- Having inherited a patient on APP from a previous treatment provider
- Endorsing a specific APP combination preference¹⁰

STUDY DESIGN AND COST

Shorter observation times and cross-sectional definitions of APP have been associated with higher APP use,^{44,68,121} which, in turn, have been related to greater medication cost (see Table 5).^{20–22,96,122–125}

DISCUSSION

The reviewed literature indicates that APP is related to patient, illness, and treatment variables that are related to greater illness acuity, severity, complexity, and chronicity. This finding seems to validate the notion that APP is prescribed for patients who are difficult to manage with standard antipsychotic monotherapy. In keeping with the association between APP and greater psychiatric comorbidity as well as higher total antipsychotic dose, nonantipsychotic cotreatment, especially anticholinergic use, has also been related to APP. Antipsychotic medication variables suggest that quetiapine, long-acting injectable formulations, and FGAs are consistently related to APP, whereas data on clozapine and olanzapine have been inconsistent. In addition, there was wide provider variability regarding APP use. This finding may be related to variations in regional or national treatment paradigms and cultures as well as to differences in patient populations, but it has also been related to lower academic and education levels, idiosyncratic practices and beliefs, and marketing or time pressure. Longer observation periods that minimize the capturing of temporary, overlapping switches have been related to less APP, whereas APP itself has been associated with greater medication treatment cost.

Patient Variables

The fact that younger age was associated with APP could be because younger age at onset is associated with greater illness severity and poorer outcomes.¹²⁶ However, by contrast, it is also possible that younger patients are undergoing more treatment changes and that cross-sectional studies captured overlapping antipsychotic switches as APP. However, arguing against the latter argument is the fact that about half of the studies reporting a significant relationship between younger age and higher APP use required a duration of APP of at least 90 days,^{36,37} 60 days,³⁵ or 28 days,³⁸ whereas the only study showing that older age was associated with APP required only a 3-day antipsychotic overlap.⁴² The finding that adolescents had more APP than children can be explained by the fact that child psychiatrists are more cautious in prescribing medications in prepubertal children, let alone multiple agents from the same class, especially combinations with little evidence in adults and absent evidence in youth. The association of male sex with APP may have to do with greater illness severity, chronicity, or dangerousness in males. The same may be true for unmarried status, which is associated both with younger age and greater illness severity/chronicity.

Information on race and ethnicity was mixed and difficult to interpret. Therefore, more data are needed that focus on the relationship between race/ethnicity and APP, taking into account other illness-related and patient-related factors as well.

Illness Variables

Illness characteristics also all point toward an association of APP with greater illness severity, acuity, complexity, chronicity, and refractoriness. Although these characteristics could justify APP, most patients receiving APP have not received a trial with clozapine,¹²⁷ a step in the treatment algorithm endorsed by most, if not all, treatment guidelines.^{24–29} However, it is also possible that at least some of the reported APP frequencies in patients with correlates that point toward greater illness severity and complexity may relate to antipsychotic switching that is under way at the time of the survey. The inconclusive results regarding substance use disorders may be caused by undisclosed differences, whether or not substance use disorders are primary or comorbid with other severe mental disorders, which needs to be pursued in future studies.

Treatment Setting and Medication Variables

Similar to patient and illness variables, treatment setting variables associated with APP also point toward greater illness severity and chronicity of those individuals who are treated with APP. The fact that an increased total antipsychotic dose is the most consistent and replicated correlate of APP raises the important question if prescribers avoid using antipsychotic doses that are significantly higher than doses used in regulatory trials and rather prefer adding a second antipsychotic to increase dopamine blockade in patients with insufficient antipsychotic response. The problem has been raised before that patients enrolled in regulatory trials that help establish the approved medication doses are atypical patients.¹²⁸ Only a few eligible patients consent to double-blind randomized trials,^{129,130} and treatment responsiveness may be greater in these highly selected populations.¹³¹ Moreover, in order not to increase adverse effect frequencies, drug makers are not interested in studying in the pivotal trials whether a dose increase in patients with insufficient response would improve if the dose were raised.¹³² Given this situation, studies should compare continuation of antipsychotic monotherapy with APP and with high-dose antipsychotic treatment, a design that has only rarely been implemented.¹³³

Several medication variables were significantly associated with APP. For example, decanoate antipsychotics, FGAs and quetiapine were associated with greater APP. The cotreatment of long-acting injectable formulations with a different antipsychotic is not uncommon, because it may be difficult to perform a fine-grained dose adjustment with injectable antipsychotics alone. The cotreatment of FGAs and second-generation antipsychotics (SGAs) was the most frequent combination in the systematic review of APP frequencies³ and may be related to clinicians' attempts to add more selective D2 blockade to SGAs, which occupy other receptors.²³ Among individual antipsychotics, quetiapine is particularly often prescribed in combination with other antipsychotics. This situation may be because quetiapine has low extrapyramidal side effects (EPS) rates across the dose range, which can be seen as an advantage when attempting to increase total net dopamine blockade. In addition, quetiapine is also used to treat nonpsychotic comorbid conditions, such as anxiety, depression, and sleep disturbances,¹³⁴ which seem to be particularly prominent in more complex and chronically ill patients, who are more likely to receive APP. Greater treatment with antidepressants, anxiolytics, and mood stabilizers was also related to APP, corresponding to the higher comorbidity described earlier. By contrast, mixed results were found in the use of clozapine or olanzapine as part of APP combinations, with some authors reporting higher^{35,68,96} and lower utilization.^{68,103} These seemingly contradictory findings may be because, on the one hand, more severely ill patients who do not even respond to

clozapine and olanzapine are predisposed to APP. On the other hand, effective treatment with clozapine or olanzapine may decrease the need for adding a second antipsychotic. Although APP was associated with greater anticholinergic use, data are missing that determine whether this is predominantly driven by the frequent SGA-FGA combinations and whether and which SGA-SGA combinations may not lead to clinically relevant EPS, necessitating anticholinergic cotreatment. The study showing less treatment discontinuation with aripiprazole when it was combined with a second antipsychotic¹⁰⁴ may be because during the initial treatment with aripiprazole its less sedating properties, coupled with its partial D2 agonism, can lead to increased restlessness or agitation, which can be mitigated by co-use of a more sedating, full D2 antagonist.

Provider and Other Variables

Studies suggest that there are considerable regional and provider differences regarding the frequency of APP use.^{55,56,59,83,115–118} Moreover, there is concern that less teaching, research, and independent continuous medical education, as well as greater attendance of programs sponsored by the pharmaceutical industry, are related to higher APP. These findings, together with previously described associations of greater perceived work pressure and less available time for patient care, endorsed also by nursing staff,¹¹⁹ highlight intervention targets for educational, hospital-based and administrative initiatives aimed at reducing inappropriate APP prescribing. Such initiatives have already shown initial success^{115,135} and are backed up by research findings from controlled studies in which 50% to 67% of patients on APP could be successfully converted to antipsychotic monotherapy without decompensation.^{136,137}

In keeping with reduced inclusion of patients undergoing active antipsychotic switches, longer observation periods and the related requirement of 1, 2, or 3 months of combined antipsychotic use to establish APP have been associated with lower APP.^{44,68,121}

In addition, APP has been associated with greater medication cost.^{20–22,96,122–125} For example, in an analysis of an outpatient Medicaid population, APP was the most expensive form of SGA use, costing up to 3 times more per patient than mono-therapy.¹⁴ In another study of 836 patients treated in New Hampshire between 1995 and 1999, the increase in the prevalence of APP from 6% to 24% resulted in an average increased medication cost of \$400/mo per patient.¹²⁵ Likewise, a prospective, naturalistic study of 846 patients started on olanzapine, quetiapine, or risperidone and followed for 1 year found that each dollar spent on the index antipsychotic was accompanied by spending an additional \$1.31 on concomitant antipsychotics for patients initiated on quetiapine, \$0.64 for risperidone, and \$0.38 for olanzapine.²¹ Similar results were reported in a randomized, placebo-controlled study of risperidone, quetiapine, or placebo in 382 patients with schizophrenia or schizoaffective disorder, in which patients received clinician's choice psychotropic cotreatment of an additional 28 days after a minimum of 14 days of monotherapy. In this trial, the mean projected cost of additional antipsychotics, making up greater than 95% of the added medications, per randomized patient during the additive-therapy phase was \$57.03 in the risperidone group and \$101.64 in the quetiapine group.²⁰

The substantially higher medication costs associated with APP make this treatment strategy with insufficient evidence base for its efficacy and safety an important target for future research and attempts at reducing irrational APP use. Because patients receiving APP have been shown to have a more complex and severe illness, any studies investigating nonmedication service costs before and after initiation of APP need to use methods that take the illness severity and chronicity into account, either by selecting appropriate comparison groups, using an appropriate mirror image design, or using sophisticated statistical methods, which use propensity score matching methods that take into consideration relevant and

directly measured patient and illness attributes that are associated with illness severity, APP, and the investigated targeted outcomes.

LIMITATIONS

The results of this systematic review have to be interpreted within its limitations. First, this was a descriptive review of studies that generally did not focus on correlates of APP, but rather focused on the reporting of APP prevalence. Therefore, the reported associations likely do not capture all of the possible associations because such analyses were either not reported or conducted in a large number of studies reporting on APP. Of 147 studies reporting on APP prevalence until 2009,³ only 88 (50.3%) included in this review reported on correlates of APP. Moreover, most studies selected specific correlates for analysis, but there has not been a comprehensive screening for potential associations, and most studies collected data on only some of the potential and relevant correlates. Furthermore, many studies were cross-sectional and may have included ongoing antipsychotic switches, correlating variables to both patients undergoing active antipsychotic switches and those with sustained APP. Therefore, future studies should focus on persistent APP (eg, >60 or 90 days) and collect data and screen for associations taking the variables summarized in this article as a guide. However, in order to perform multivariate analyses, such studies also need to be large enough. Furthermore, associations do not prove causality. Therefore, future studies are needed that interview clinicians and patients and ask directly about the reasons for the use of APP and about barriers to convert patients to antipsychotic monotherapy. The latter is particularly relevant because, as mentioned earlier, an emerging body of evidence suggests that 50% to 67% of patients receiving longer-term APP can safely be converted to antipsychotic monotherapy regimes.^{136,137}

Nevertheless, despite these limitations, this is the first systematic review summarizing correlates of APP and showing that greater illness severity, chronicity, and complexity are all associated with APP, underscoring the need for the discovery of novel mechanism of antipsychotic treatment, so that rational polypharmacy can be used as a pharmacologic tool to help those patients with limited response to standard antipsychotic monotherapy.

SUMMARY

Despite insufficient evidence for its safety and effectiveness, APP has remained a common treatment strategy in the management of patients with psychotic disorders, especially those with schizophrenia spectrum disorders. APP is related to patient, illness, and treatment variables that all point toward a greater illness acuity, severity, and chronicity. However, there also seem to be provider characteristics at play that suggest that, at least, some APP may be idiosyncratic or unfounded. The latter idea is supported by studies suggesting that more than half of patients on longer-term APP can be safely and successfully converted to antipsychotic monotherapy. Although not a topic of this review, adverse effect patterns seem to be less homogeneous and depend on specific combinations, with some increasing adverse effect burden, some not affecting adverse effects, and others reducing specific adverse effects, even in the absence of lowering the dose of the initial antipsychotic.³¹

However, given the established effectiveness of clozapine for treatment-refractory psychotic and mood symptoms,^{138,139} at least when adequately dosed,¹³⁹ the risks and uncertainties regarding APP have to be weighed against the well-established risk/benefit ratio of clozapine treatment. Although difficult to design, conduct, and obtain funding for, randomized controlled combination and discontinuation studies are necessary before the role of APP in the management of schizophrenia and other severe psychotic disorders can be determined. In addition to controlled trials, direct investigations should focus on reasons for choosing and continuing APP regimes, and on identifying and comprehensively

characterizing patients benefiting from APP who cannot be converted to antipsychotic monotherapy, including that with clozapine. Such studies may help shed light on biological underpinnings of treatment refractoriness and on dysfunctional, nondopaminergic pathways that could help identify novel treatment targets.

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KEY POINTS

- Despite insufficient evidence for its safety and effectiveness, antipsychotic polypharmacy (APP) has remained a common treatment strategy in the management of patients with psychotic disorders, especially those with schizophrenia spectrum disorders.
- The risks and uncertainties regarding APP have to be weighed against the well-established risk-benefit ratio of clozapine treatment.
- Concerns with APP include the possibility of higher than necessary total chlorpromazine equivalent dosages, increased acute or long-term side effects, anticipated (or unanticipated) drug-drug interactions, increased rates of noncompliance caused by an increased complexity of drug regimens, difficulties in determining cause and effect of multiple treatments, and substantially higher cost.
- APP is related to patient, illness, and treatment variables that all point toward a greater illness acuity, severity, and chronicity.
- However, some studies suggest that about half of the patients on APP can be successfully converted to antipsychotic monotherapy, indicating that the use of APP may not be required in a relevant number of cases.
- Future randomized controlled studies are needed to understand risks and benefits of APP in comparison with antipsychotic monotherapy and, possibly, high dose antipsychotic monotherapy.

Table 1

Potential reasons for and concerns about APP

Potential Reasons	Potential Concerns
Active cross-titration	Higher than necessary total dosage
Aborted cross-titration	Increased acute side effects
Enhancement of efficacy	Increased long-term side effects
Speeding up of efficacy	Loss of atypicality
Treatment of different symptom domain (eg, agitation, cognition, negative symptoms)	Drug-drug interactions (known and unforeseen)
Treatment of comorbidity (eg, insomnia, anxiety, depression)	Increased risk of nonadherence
Reduction of dose of first antipsychotic	Difficulty determining cause and effect
Reduction of adverse effects of first antipsychotic	Lack of evidence base
Different route of administration	Increased mortality
Combining complementary pharmacologic and side effects profiles	Cost
Poor communication between services	
Patient's/family's choice/pressure	
Prescriber habit	
Marketing influences	

Table 2

Patient variables associated with APP

Variable	Studies	
Younger age	Aparasu et al, ³² 2009 Molina et al, ³³ 2009 Lerma-Carrillo et al, ³⁴ 2008 Morrato et al, ³⁵ 2007 Kreyenbuhl et al, ³⁶ 2007 Kogut et al, ³⁷ 2005 Biancosino et al, ⁵ 2005 Jaffe and Levine 2003 ³⁸ Weissman et al, ³⁹ 2002 Leslie et al, ⁴⁰ 2001 Raschetti et al, ⁴¹ 1993	Opposite: Lass et al, ⁴² 2008 adolescents > children: Constantine et al, ⁴³ 2010
Male sex	Molina et al, ³³ 2009 Lerma-Carrillo et al, ³⁴ 2008 Morrato et al, ³⁵ 2007 Biancosino et al, ⁵ 2005 Ganguly et al, ⁶⁸ 2004 Lelliott et al, ⁵² 2002 Fourrier et al, ⁵³ 2000	Opposite: Kreyenbuhl et al, ⁷⁰ 2007
White/non-Latino	Covell et al, ⁴⁴ 2002 Leslie and Rosenheck, ⁴⁰ 2001	No differences between Whites and Blacks: Connolly et al, ⁴⁵ 2007
African American race	Jaffe and Levine, ³⁸ 2003	Opposite: Kreyenbuhl et al, ³⁶ 2007
Unmarried	Santone et al, ⁴⁶ 2011 Kreyenbuhl et al, ³⁶ 2007 Biancosino et al, ⁵ 2005 Covell et al, ⁴⁴ 2002	

Table 3

Illness variables associated with APP

Variable	Studies	
Schizophrenia/schizoaffective disorder	Millier et al, ⁴⁷ 2011 Santone et al, ⁴⁶ 2011 Procyshin et al, ⁴⁸ 2010 Castberg et al, ⁴⁹ 2008 Correll et al, ⁵⁰ 2007 Morrato et al, ³⁵ 2007 Biancosino et al, ⁵ 2005 Procyshin et al, ⁵¹ 2004 Lelliot et al, ⁵² 2002 Weissman et al, ³⁹ 2002 Fourrier et al, ⁵³ 2000	
Psychotic disorder	Constantine et al, ⁴³ 2010 Aparasu et al, ³² 2009	
Earlier illness onset	Millier et al, ⁴⁷ 2011	
Longer illness duration	De Hert et al, ⁵⁴ 2006 Barbui et al, ^{55,76} 2006 Sim et al, ⁵⁶ 2004 Janssen et al, ⁵⁷ 2004 Correll et al, ⁵⁸ 2003 Chong et al, ⁵⁹ 2004 Yip et al, ⁶⁰ 1997	Opposite: Biancosino et al, ⁵ 2005
Greater illness acuity or severity	Millier et al, ⁴⁷ 2011 Stroup et al, ⁶¹ 2009 Kreyenbuhl et al, ^{36,70} 2007 De Hert et al, ⁵⁴ 2006 Barbui et al, ^{55,76} 2006 Centorrino et al, ⁶² 2005 Biancosino et al, ⁵ 2005 Janssen et al, ⁵⁷ 2004 Weinmann et al, ⁶³ 2004 Schumacher et al 2004 Tapp et al, ⁷ 2003 Brunot et al, ⁶⁵ 2002 Leslie and Rosenheck, ⁴⁰ 2001 Fourrier et al, ⁵³ 2000	Not relapse: Millier et al, ⁴⁷ 2011
Less improvement	Rupnow et al, ²⁰ 2007	
Less illness insight	Santone et al, ⁴⁶ 2011 Millier et al, ⁴⁷ 2011	
Treatment resistance	Tomasi et al, ⁶⁶ 2006 Barbui et al, ^{55,76} 2006	
History of violence	Yip et al, ⁶⁰ 1997	
More negative symptoms	Morrato et al, ³⁵ 2007	
More psychiatric comorbidity	Morrato et al, ³⁵ 2007	
Comorbid depression	Kreyenbuhl et al, ³⁶ 2007	
Comorbid nicotine abuse	Paton et al, ⁶⁷ 2004	
Comorbid substance abuse	Weinmann et al, ⁶³ 2004 Leslie and Rosenheck, ⁴⁰ 2001	Opposite: Kreyenbuhl et al, ³⁶ 2007 Ganguly et al, ⁶⁸ 2004

Table 4

Treatment setting and medication variables associated with APP

Variable	Studies		
Involuntary treatment	Lelliott et al, ⁵² 2002		
Hospitalization	Gilmer et al, ⁶⁹ 2007 Kreyenbuhl et al, ⁷⁰ 2007 Weinmann et al, ⁶³ 2004	Brunot et al, ⁶⁵ 2002 Fourrier et al, ⁵³ 2000 Tibaldi et al, ⁷¹ 1997	
Longer inpatient stay	Ghio et al, ⁷² 2011 Gilmer et al, ⁶⁹ 2007 Centorrino et al, ⁷³ 2004 Yip et al, ⁶⁰ 1997	Opposite: Molina et al, ³³ 2009	
Longer treatment duration	Ganguly et al, ⁶⁸ 2004 Fourrier et al, ⁵³ 2000		
History of multiple antipsychotic switches	Jaffe and Levine, ³⁸ 2003		
Nonadherence/partial adherence	Ahn et al, ⁷⁴ 2008 Simon et al, ⁷⁵ 2005		
APP at baseline	Barbui et al, ⁷⁶ 2006 Biancosino et al, ⁵ 2005 Schumacher et al, ⁶⁴ 2003		
Higher total dose	Ghio et al, ⁷² 2011 Procyshyn et al, ⁴⁸ 2010 Ranceva et al, ⁷⁷ 2010 Correll et al, ¹⁸ 2009 Elie et al, ⁷⁸ 2010 Centorrino et al, ⁷⁹ 2008 Hung and Cheung, ⁸⁰ 2008 Paton et al, ⁸¹ 2008 Kreyenbuhl et al, ³⁶ 2007 Correll et al, ⁵⁰ 2007	Wheeler et al, ⁸² 2006 Carnahan et al, ⁸⁴ 2006 Florez Menendez et al, ⁸⁵ 2004 Centorrino et al, ⁷³ 2004 Kogut et al, ³⁷ 2005 Linden et al, ⁸⁶ 2004 Humberstone et al, ⁸³ 2004 Sim et al, ⁵⁶ 2004 Bingefors et al, ⁸⁷ 2003	Suzuki et al, ⁸⁸ 2003 Centorrino et al, ⁸⁹ 2002 Harrington et al, ⁹⁰ 2002 Lelliott et al, ⁵² 2002 Chong et al, ⁹¹ 2000 Tognoni, ⁹² 1999 Galletly and Tsourtos 1997 ⁹³ Tibaldi et al, ⁷¹ 1997 Rosholm et al, ⁹⁴ 1994 Remington et al, ⁹⁵ 1993
Quetiapine treatment	Rupnow et al, ²⁰ 2007 Correll et al, ⁵⁰ 2007 Faries et al, ⁹⁶ 2005	Ganguly et al, ⁶⁸ 2004 Centorrino et al, ⁷³ 2004	Ereshefsky, ⁹⁸ 1999
Depot antipsychotic treatment	Hori et al, ⁹⁹ 2006 Xiang et al 2008 Chiu et al, ¹⁰¹ 1991		
First-generation antipsychotic treatment	Elie et al, ⁷⁸ 2010 Divac et al, ¹⁰² 2007 Correll et al, ⁵⁸ 2006		Florez Menendez et al, ⁸⁵ 2005 Ganguly et al, ⁶⁸ 2004
Clozapine treatment	Morrato et al, ³⁵ 2007 Ganguly et al, ⁶⁸ 2004		Opposite: Taylor et al, ¹⁰³ 2008
Olanzapine treatment	Faries et al, ⁹⁶ 2005		Opposite: Ganguly et al, ⁶⁸ 2004
Lower aripiprazole discontinuation	Shahajan et al, ¹⁰⁴ 2008		
Anticholinergic treatment	Ghio et al, ⁷² 2011 Hong and Bishop, ¹⁰⁵ 2010 Kreyenbuhl et al, ³⁶ 2007 Xiang et al, ¹⁰⁰ 2008 De Hert et al, ⁵⁴ 2006 Chakos et al, ¹⁰⁶ 2006 Florez Menendez et al, ⁸⁵ 2005	Carnahan et al, ⁸⁴ 2006 Ganguly et al, ⁶⁸ 2004 Sim et al 2004 ⁵⁶ Procyshyn et al, ¹⁰⁷ 2001 Taylor et al, ¹⁰⁸ 2000 Tognoni et al, ⁹² 1999	Brambilla et al, ¹⁰⁹ 1999 Hida et al, ¹¹⁰ 1997 Kivet 1995 Clark and Holden, ¹¹² 1987 Morgan and Gopalaswamy, ¹¹³ 1984 Mason et al, ¹¹⁴ 1977
Antidepressant treatment	Millier et al, ⁴⁷ 2011 Kreyenbuhl et al, ⁷⁰ 2007		
Anxiolytic treatment	Millier et al, ⁴⁷ 2011		

Variable	Studies
	Centorrino et al, ⁷⁹ 2008 Kreyenbuhl et al, ⁷⁰ 2007 De Hert et al, ⁵⁴ 2006
Mood stabilizer treatment	Centorrino et al, ⁷⁹ 2008 Kreyenbuhl et al, ³⁶ 2007 Ganguly et al, ⁶⁸ 2004

Table 5

Provider and other variables associated with APP

Variable	Studies	
Provider Characteristics		
Region/country/prescriber	Patrick et al, ¹¹⁵ 2006 Barbui et al, ^{55,76} 2006 Sim et al, ⁵⁶ 2004 Chong et al, ⁵⁹ 2004	Humberstone et al, ⁸³ 2004 Muscettola et al, ¹¹⁶ 1987 Muijen et al, ¹¹⁷ 1987 Edwards and Kumar, ¹¹⁸ 1984
Metropolitan area	Aparasu et al, ³² 2009	
Nonteaching hospital, less research involvement	Baandrup et al, ¹¹⁹ 2010 Johnson and Wright 1990 ¹²⁰	
Attendance at educational programs sponsored by a pharmaceutical company	Kreyenbuhl et al, ⁷⁰ 2007	
Less attendance at local continuous medical education activities	Baandrup et al, ¹¹⁹ 2010	
Treatment by same doctor for >2 y	Kreyenbuhl et al, ⁷⁰ 2007	
More senior staff vs trainees	Correll et al, ¹⁰ 2011	
Specific APP preference	Correll et al, ¹⁰ 2011	
Inherited APP by previous provider, greater reliance on previous provider's APP recommendation	Correll et al, ¹⁰ 2011	
Time pressure, workload	Baandrup et al, ¹¹⁹ 2010	
Other Characteristics		
Shorter study observation periods	Kreyenbuhl et al, ¹²¹ 2006 Ganguly et al, ⁶⁸ 2004 Covell et al, ⁴⁴ 2002	
Greater medication cost	Baandrup et al, ¹²² 2011 Zhu and Ascher-Svanum, ²¹ 2008 Rupnow et al, ²⁰ 2007 Valuck et al, ¹²³ 2007	Stahl et al, ²² 2006 Faries et al, ⁹⁶ 2005 Loosbrock et al, ¹²⁴ 2003 Clark et al, ¹²⁵ 2002