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Atypical antipsychotic agents for the schizophrenia prodrome: Not a clear first choice

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Abstract. Pharmacologic intervention at the earliest stages of suspected psychotic illness is an intuitively appealing concept and a logical extension of the current approach to many other diseases of the central nervous system. Atypical antipsychotic agents (ATAPs) seem to be a reasonable choice for early intervention because existing pre-clinical data suggest that they have pharmacologic properties which might confer 'neuroprotection'. However, a critical analysis of the results of structured clinical investigations which have explored the use of ATAPs for new-onset psychotic symptoms raises safety concerns and does not support pre-medication in this setting as a preventive strategy. Caution in current practice is therefore appropriate, underscoring the need for much additional clinical research.

Keywords: Schizophrenia prodrome, pre-medication, early psychosis, atypical antipsychotics, neuroprotection

1. Introduction

Over the past several years, a voice has emerged in the international psychiatric community recommending early prescription of the atypical antipsychotic agents (ATAPs) for adolescents and young adults who appear to show signs consistent with a schizophrenia prodrome. Early use is predicated on the possibility that ATAPs may prevent progression to full-blown psychotic illness in this high-risk population. This trend has been encouraged despite a paucity of data which clearly support the effectiveness of these agents for this indication, and despite evidence of adverse side effects including, but not limited to: obesity, hyperlipidemia, metabolic syndrome, increased rates of type II diabetes mellitus and extrapyramidal syndromes, both acute and chronic [1,23]. These circumstances prompted this literature review, focusing on the five published studies that have explicitly addressed the preventative efficacy of the most widely prescribed ATAPs in structured (i.e., non-anecdotal) clinical settings.

Formal meta-analysis using pooled data was neither appropriate nor possible given the small numbers of subjects involved overall and the substantial differences in baseline clinical features and outcome measures chosen by the various investigators. We describe the reported rates of conversion to psychosis

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after pharmacologic intervention with special attention to baseline clinical characteristics, medication-adherence, safety issues and the conflicting conclusions of current research.

2. Brief review of literature

A recent study by Cornblatt et al. from the Recognition and Prevention (RAP) program at the North Shore-Long Island Jewish Health System used naturalistic methodology to explore the clinical responses to ATAPs and antidepressant agents in adolescents and young adults at high-risk of developing psychotic illness [5]. Over 50% of adolescents and young adults referred to their facility for subspecialty psychiatric management of new-onset psychotic symptoms had already been prescribed an ATAP by physicians in their referral network [5], indicating the widespread nature of "off-label" use in this setting.

Contrary to the conclusions of other recent studies which claim that early prescription of ATAPs may be useful in preventing schizophrenia [8,13,14,17,21], Cornblatt et al. concluded that these agents not only did not prevent progression, but were associated with a markedly *greater* conversion rate as well as high rates of polypharmacy and medication non-adherence [5]. In contrast, patients with early-onset psychotic symptoms who were prescribed antidepressants in their study seldom converted to frank psychosis over multiple years of observation, and tolerated these medications generally well. The RAP group's work does not provide a clear explanation for the poor outcomes associated with use of ATAPs in their study, nor proof that antidepressant medication is appropriate or effective in preventing progression of psychotic illness. In addition, the naturalistic methodology used reflects a set of uncontrolled observations in a diverse patient population. Nevertheless, the important possibility is raised that under conditions perhaps more reflective of routine clinical practice, early prescription of ATAPs for suspected schizophrenia prodrome may be associated with poly-pharmacy and high rates of medical non-compliance that contribute to poor long-term outcomes.

Controlled studies. There have been very few controlled studies addressing the preventative efficacy of ATAPs in schizophrenia prodrome. Do the data demonstrate the effectiveness of ATAPs in preventing or delaying disease progression? The study of McGorry et al. from the Personal Assessment and Crisis Evaluation (PACE) Clinic in Melbourne, Australia was the first to evaluate the possibility that an ATAP might prevent or delay disease progression in a high risk population already exhibiting moderate, non-sustained positive symptoms [17]. Patients received one of two therapies: needs-based intervention (NBI), which included symptom-prompted pharmacotherapy plus supportive psychotherapy; or standard therapy *plus* a combination of low-dose risperidone (mean dose 1.3 mg/day) and specially-assigned cognitive, behavioral and stress management therapies. The latter intervention was defined as specific preventive intervention (SPI). The chief weaknesses of their study included: low numbers of patients at the time of randomization (59 total; 28 receiving NBI and 31 SPI), substantial non-adherence in the SPI group (only 45% of those 31 patients were fully compliant with prescribed medication) and incomplete blinding [17].

Within the first 6 months of post-intervention patient observation. McGorry et al. observed that fewer patients receiving the SPI converted to psychosis as defined by attainment of supra-threshold scores on standardized scales that quantified different aspects of positive symptoms and signs. This apparent advantage was marginally statistically significant ($p = 0.03$) at 6 months after start of intervention, but was lost at 12 months follow-up because of the conversion to psychosis of an additional 3 of the 31 patients assigned to receive SPI. It is noteworthy that the patients receiving SPI had greater psychosocial contact – therapy sessions plus number of evaluations – than their NBI counter-parts, and a possible

treatment effect related to the more intensive cognitive, behavioral and stress management therapies could not be distinguished from the impact of risperidone. McGorry et al. did not report any significant adverse side effects linked with ATAPs. The authors speculated that a larger study involving more medication-adherent subjects might have demonstrated a sustained benefit of the ATAP-associated SPI in slowing or eliminating conversions to psychosis, but their data do not support this. The key parameters of the study are summarized in Table 1.

Lieberman et al. have taken a leading role in promulgating the view that atypical antipsychotic agents may exert a "neuroprotective" effect [8,11,13]. In an often-quoted longitudinal study comparing the effects of the ATAP olanzapine with haloperidol in individuals presenting with psychotic symptoms, the authors described superior clinical functional status and better preservation of cortical volume in patients receiving olanzapine [6,8,14,20]. The novel neuro-imaging component of this study was predicated on earlier observations that patients with schizophrenia prodrome who later progressed to full-blown schizophrenia may exhibit subtle, regionally specific decrements in cortical thickness [12,26]

Table 1
Summary of studies reviewed

	Study type/ methodology	Intervention tested	Primary outcome measure(s)	Avg age (yrs)	Drop-out rates/ non-adherence	Conversion to psychosis (or other outcome)	General comments
Cornblatt et al. RAP (2007)	Naturalistic	Comparison of ATAPs and antidepressants in high-risk patients	Conversion to psychosis	16	ATAP: 61% Antidepressants: 20%	39% (11/28) 0% (0/20)	All patients converting to psychosis received ATAP
McGorry et al. PACE (2002)	Randomized, partial blinding, non-placebo ctrl.	Specific intervention (SPI; low dose risperidone) vs. needs-based therapy (NBI)	Conversion to psychosis	20	SPI c ATAP: 55% NBI: 0%	19% (6/31) 36% (10/28)	No statistically significant sustained differences between and SPI and NBI
Lieberman et al. (2005)	Randomized, double blind, placebo ctrl.	Olanzapine vs. haloperidol	Volume change on brain MRI + functional outcome	24	Olanzapine: 36% Haloperidol: 40%	N/A	Brain volume reduction less and clinical status better with olanzapine, but the haldoperidol group may have been more "ill" at baseline
McGlashan et al. PRIME (2006)	Randomized, double blind, placebo ctrl.	Olanzapine vs. placebo	Conversion to psychosis	17.5	Olanzapine: 55% Placebo: 35%	16% (5/31) 38% (10/29)	No statistically significant reduction in conversion rate with ATAP

ATAP = atypical antipsychotic; NBI = needs-based intervention (designation particular to the study of McGorry et al.); SPI = specific preventive intervention (designation particular to the study of McGorry et al.).

and hippocampal volume [2,29], "Antipsychotic drug effects on brain morphology in first-episode psychosis" by Lieberman et al. was a relatively large, prospective, multi-center, randomized, controlled trial [14]. However, careful review of the baseline clinical characteristics published within that study indicates that this was not a cohort of individuals with "first-episode psychosis" as the title implies. They were, in fact, a heterogeneous collection of patients with wide-ranging psychotic symptoms of variable duration who had presented to emergency departments, inpatient wards or outpatient facilities at several different medical centers in 4 countries with a variety of specific diagnoses, including: schizophrenia, schizophreniform disorder and schizoaffective disorder.

The multitude of participating centers and the lack of clear operational diagnostic criteria used in recruiting patients into their study raises concern. The treatment groups actually differed in the percentage of patients with schizophrenia (as opposed to schizophreniform or schizoaffective disorders), with only 56.1% schizophrenics in the olanzapine-treated group and 73.4% schizophrenic in the haloperidol-treated group [14]. This discrepancy is important because there are expected differences in the rates and manner of progression of these different psychiatric entities and there is no evidence that the cerebral atrophic changes observed in schizophrenics are seen in patients with other idiopathic psychotic illnesses, such as schizoaffective disorder.

Although the treatment arms of the study appear to have been well-matched with respect to patient age, sex and duration of prior anti-psychotic treatment (see Lieberman et al., Table 1; p. 364), there was a potentially biasing imbalance with respect to the *duration of illness prior to initiation of treatment* (54.11 ± 50.7 weeks in olanzapine treated patients and 77.3 ± 61.6 weeks in patients receiving haloperidol). Even with the substantial standard deviations associated with each subgroup's mean, this difference reached a high level of statistical significance with $p = 0.007$ [14]. Duration of illness prior to treatment is a prognostic variable that correlates positively with poor outcomes [15,19]. Taken together, these discrepancies in baseline characteristics suggest strongly that the haloperidol-treated patients in the landmark study by Lieberman et al. were, at baseline, more psychiatrically ill than those receiving olanzapine – and had been ill for longer periods of time. These unmatched differences in the degree and duration of psychiatric illnesses between the olanzapine and haloperidol groups strongly suggest an alternative explanation for the differential clinical and morphological outcomes that were interpreted by the authors as a possible treatment effect of olanzapine. (The possibility of an actual detrimental effect of haloperidol is another alternative explanation entertained by the authors [14].)

In a placebo-controlled pilot study published in 2003, Woods et al. reported that olanzapine, 5–15 mg daily, was associated with greater symptomatic improvement, and there was a statistically significant treatment-by-time interaction for change from baseline psychotic symptoms on the Scale of Prodromal Symptoms (SPS) [18,30]. This publication was essentially a report on the first 8 weeks experience of the multi-center Prevention through Risk Identification, Management and Education (PRIME) clinics' study, later published in its entirety in 2006 by McGlashan et al. [16]. The latter is perhaps the most rigorous of the four controlled studies published to date which have specifically addressed efficacy and side-effects of ATAPs in the management of the schizophrenia prodrome; it was double-blinded, placebo controlled, and there were no major imbalances apparent in baseline clinical characteristics. However, the numbers of patients recruited into the PRIME study were small ($N = 60$) and after excluding 27 patients who dropped out for reasons other than conversion to psychosis – some of whom were non-compliant with medication – the final efficacy analysis involved only 14 olanzapine-treated versus 19 placebo controls. There was a very high drop-out rate for both the olanzapine-treated (32%) and placebo-treated (23%) patients. In addition, very substantial increases in weight were observed in the olanzapine-treated patients (mean of 13% weight gain), a highly statistically significant change that evolved during the periods of

follow-up observation and was therefore a potential challenge to double-blinding. Using either protocol-specific or intention-to-treat analyses, the authors were unable to demonstrate any statistically significant differences between these groups as to efficacy in preventing conversion to psychosis, only a trend favoring olanzapine that the authors interpreted as more likely an effect of this drug on *delaying* onset of psychosis [16]. As the authors acknowledged, however, the study was not really powered to distinguish delay versus prevention.

3. Discussion

The controlled data presented in the studies of McGorry et al. [17], Woods et al. [30] and McGlashan et al. [16] do not provide solid evidence of the effectiveness of ATAPs in preventing the development of psychotic illness as defined by DSM-IV criteria in medication-adherent patients. Neither does the study by Lieberman et al. [14] firmly support differential treatment effects on brain volume or clinical status of an atypical versus a first generation antipsychotic agent in patients in the early stages of psychotic illnesses. Indeed, if we combine the numbers of patients involved in published controlled comparisons (the 4 studies reviewed above), it is clear that only 62 ATAP-treated patients and 57 comparators have been evaluated. Of these, an average of 55% of patients receiving an ATAP were non-compliant or had dropped out of the studies for reasons other than conversion to psychosis (Table 2). Intention-to-treat analyses and calculation of relative risks ratios, both of which were used in these controlled studies, are of questionable value in the presence of such small starting numbers and such high intra-study drop-out rates. Both adequate power and adequate study duration are essential factors in judging the effectiveness of controlled interventions, particularly in light of the report from Cornblatt et al. and others, which conclude that conversion to psychosis may occur in this dynamic population over several years of observation [11,23].

The substance abuse histories of the subjects are another source of significant bias not consistently addressed in the studies discussed above. Most of the investigations reviewed in this article indicated that recent or ongoing substance abuse or dependence was a basis for exclusion from the study. For example, in the *Methods Section* of the study by Lieberman et al. (see [14], pp. 362–363), the authors indicate

Table 2
Rates of non-adherence or non-conversion related-drop-outs

Cornblatt et al.	ATAP: 17/28 (61%)
RAP (2007)	Antidepressant: 4/20 (20%)
McGorry et al.	ATAP: 17/31 (55%)
PACE (2002)	Control: 0/28 (0%)
Lieberman et al.	ATAP: 47/129 (36%)
HGDH (2005)	Haloperidol: 52/131 (40%)
McGlashan et al.	ATAP: 17/31 (55%)
PRIME (2006)	Control: 10/29 (35%)

This table lists the number of patients who were non-adherent with study medication or who "dropped out" of the studies in relation to the treatment regimen (numerators). ATAP = atypical antipsychotic. Note the small total numbers of patients involved in the treatment and control arms of the various studies (denominators), and the high percentage – generally >50% – of ATAP-associated non-adherence or "dropping out".

that any substance dependence within 1 month before study entry was an across-the-board exclusion criterion; however, no information is offered as to the means by which long-term substance abuse or dependence histories were compared or how substance exposure was monitored during the execution of the up to 104 weeks of follow-up observation, a period over which follow-up brain imaging was used to explore difference in cerebral atrophy in their study. This is a critical consideration in light of the well-documented but under-appreciated overlap between schizophrenia and various forms of substance abuse and dependence [4,10,24,25]. It is probably the single-most prevalent confounder in studies of the sort reviewed here. In particular, studies which intend to discriminate subtle differences in cerebral volume in relation to therapeutic interventions (for example, a decrease by 0.5% in the olanzapine-treated patients versus a decrease by 1.9% for haloperidol-treated patients in the study of Lieberman et al. [14]) must assure baseline comparability and rigorously control for those forms of substance abuse and dependence that are credibly linked with macroscopic cerebral morphologic changes, most notably alcohol, cocaine, methamphetamine and even nicotine [3,9,22,27,28].

4. Summary and conclusion

The results from the available controlled trials reviewed above are in line with several of the conclusions of the naturalistic study by Cornblatt et al. discussed at the beginning of this paper. That is, early prescription of ATAPs to adolescents and young adults seeking medical attention for prodromal psychotic symptoms is associated with high rates of medication non-adherence (see Table 2). Additionally, the introduction of ATAPs was not associated with reduction in the rate of conversion to formal psychosis beyond that explainable by chance and/or the introduction of bias secondary to baseline imbalances, inadequate blinding or even differential psychosocial supports.

Much additional clinical research is needed. In particular, future interventional studies must involve substantially larger numbers of prodromal patients, notwithstanding the major challenges presented by the high drop-out rates, the often conspicuous weight gain and the poor adherence to medication in this population. Rigorous study of therapies with demonstrably better tolerability and less severe side effects than ATAPs – including non-pharmacologic interventions – should be supported.

While the concept of preventive pharmacotherapy in managing psychotic illness is compelling [7], the ATAPs are certainly not a clear first choice for schizophrenia prodrome. We suggest caution in making any assumptions that justify changes in prescription-writing behavior when it involves patients who are at high risk for developing long-term psychotic illnesses but have never demonstrated sustained psychosis (psychotic illness by DSM-IV criteria). This would include but is not limited to persons with suspected schizophrenia prodrome. *Even in the hands of experienced investigators using detailed screening protocols in controlled settings, only one-quarter to one-third of high-risk patients converted to full-blown psychosis* (see Table 3). Consequently, if early use of ATAPs continues as a quasi-standard of care for new-onset psychotic symptoms, a large majority of these often young individuals will be exposed unnecessarily to poorly defined but likely substantial risks, including but not limited to obesity, hyperlipidemia, metabolic syndrome, increased rates of type II diabetes mellitus and extrapyramidal syndromes, both acute and chronic. Considerations of safety must come first when the preventative efficacy of these agents remains so poorly defined.

Table 3
Average conversion-to-psychosis rates for all randomized patients

Cornblatt et al. RAP (2007)	25%
McGorry PACE (2002)	27%
McGlashan PRIME (2006)	27%

This table gives the average conversion-to-psychosis rate for all patients – both ATAP-treated and comparators – to emphasize the relatively low total rate of conversion to psychosis in persons identified as "high-risk" in the various studies reviewed. Where data was available in this regard, they were remarkably consistent in identifying conversion rates between 25 and 30%, generally lower than those quoted previously in the literature based on retrospective reviews and anecdotes. See discussion of individual studies for details.

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