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Prevalence and correlates of antipsychotic polypharmacy in children and adolescents receiving antipsychotic treatment*

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Abstract

Antipsychotic polypharmacy (APP), which is common in adults with psychotic disorders, is of unproven efficacy and raises safety concerns. Although youth are increasingly prescribed antipsychotics, little is known about APP in this population. We performed a systematic PubMed search (last update 26 January 2013) of studies reporting the prevalence of APP in antipsychotic-treated youth. Summary statistics and statistical tests were calculated at the study level and not weighted by sample size. Fifteen studies (*n*=58 041, range 68–23 183) reported on APP in youth [mean age=13.4±1.7 yr, 67.1±10.2% male, 77.9±27.4% treated with second-generation antipsychotics (SGAs)]. Data collected in these studies covered 1993–2008. The most common

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Statement of Interest

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diagnoses were attention-deficit hyperactivity disorder (ADHD; 39.9±23.5%) and conduct disorder/oppositional defiant disorder (CD/ODD; 33.6±24.8). In studies including predominantly children (mean age=<13 yr, *N*=5), the most common diagnosis were ADHD (50.6±25.4%) and CD/ODD (39.5±27.5%); while in studies with predominantly adolescents (mean age =≥13 yr, *N*=7) the most common diagnoses were schizophrenia-spectrum disorders (28.6±23.8%), anxiety disorders (26.9±14.9%) and bipolar-spectrum disorders (26.6±7.0%), followed closely by CD/ODD (25.8±17.7). The prevalence of APP among antipsychotic-treated youth was 9.6±7.2% (5.9±4.5% in child studies, 12.0±7.9% in adolescent studies, *p*=0.15). Higher prevalence of APP was correlated with a bipolar disorder or schizophrenia diagnosis (*p*=0.019) and APP involving SGA+SGA combinations (*p*=0.0027). No correlation was found with APP definition [≥1 d (*N*=10) *vs.* >30–≥90 d (*N*=5), *p*=0.88]. Despite lacking safety and efficacy data, APP in youth is not uncommon, even in samples predominantly consisting of non-psychotic patients. The duration, clinical motivations and effectiveness of this practice require further study.

Keywords

Adolescents; antipsychotics; attention deficit-hyperactivity disorder; children; combination; disruptive behaviour disorders; paediatric; polypharmacy

Introduction

Psychotropic medication polypharmacy is common in the treatment of psychiatric disorders (Faries *et al.* 2005). Among different combinations, antipsychotic polypharmacy (APP) has received the most attention. Especially controversial is the fact that a fairly large number of patients with schizophrenia-spectrum disorders receive APP, despite lack of sound evidence for its efficacy (Correll *et al.* 2009a; Goodwin *et al.* 2009) and concerns about increased acute and long-term adverse effect burden and cost (Gallego *et al.* 2012a,b). In adult psychiatric populations, 7–50% of antipsychotic-treated patients receive APP, with variations in patient population characteristics, setting and APP definition (Faries *et al.* 2005; Ganguly *et al.* 2004; Kreyenbuhl *et al.* 2006). In a recent systematic review of APP across 147 studies and 1 418 163 adults (82.9% with a diagnosis of schizophrenia), the median prevalence across cultures and four decades was 19.6% (Gallego *et al.* 2012a).

In adults, APP has been associated with several patient, illness treatment and environmental factors (Correll & Gallego 2012). Potential reasons for APP include a diagnosis of schizophrenia (Messer *et al.* 2006), greater illness severity, longer illness duration and increased hospitalization rates and duration (Centorrino *et al.* 2004; Gilmer *et al.* 2007). Potential consequences of APP include greater adverse effect burden (Gallego *et al.* 2012b; Jerrell & McIntyre, 2008; McIntyre & Jerrell, 2008), higher total antipsychotic doses (Bingefors *et al.* 2003; Elie *et al.* 2009; Hung & Cheung, 2008) and treatment cost (Rupnow *et al.* 2007; Stahl & Grady, 2006). In adults, APP is used in an effort to enhance or accelerate antipsychotic efficacy, treat symptoms other than psychosis (Pandurangi & Dalkilic, 2008) or reduce the dose of the first antipsychotic without loss of overall efficacy (Correll & Gallego, 2012). APP also commonly occurs during antipsychotic cross-titration and after an aborted antipsychotic switch (Stahl & Grady, 2004).

As in adults, there has been a substantial increase in the use of antipsychotics, predominantly atypical or second-generation antipsychotics (SGAs) among children and adolescents (Olfson *et al.* 2006, 2012). In this age group, antipsychotics are prescribed for a variety of mental disorders, including psychotic, affective, impulse-control, externalizing behavioural and tic disorders (Correll *et al.* 2011; Olfson *et al.* 2006, 2012). Although APP may be lower in specific populations, such as patients with a first psychotic episode (Castro-Fornieles *et al.* 2008), APP rates have been rising in such populations as well (Nielsen *et al.* 2010a,b).

Despite mounting evidence for the efficacy of antipsychotics in paediatric populations (Fraguas *et al.* 2011; Zuddas *et al.* 2011), concerns exist over increasing antipsychotic use by youth, including the fact that clinical indications for the prescription of antipsychotics are not always clear. In particular, high prescription rates for aggressive spectrum disorders, coupled with potential under-utilization of non-pharmacological treatments have called into question the use of one, let alone, two concurrently prescribed antipsychotics (Crystal *et al.* 2009). Moreover, paediatric patients are generally more sensitive to medication adverse effects (Correll, 2008). Even short-term exposure to single antipsychotic treatment can cause dramatic weight gain and metabolic abnormalities (Correll *et al.* 2009b). Because increased adverse effects have clearly been associated with APP in adults (Gallego *et al.* 2012b), there is concern that APP may also increase the risk of adverse effects in the vulnerable paediatric population.

Scant research has focused on prevalence and predictors of combined antipsychotic use in children and adolescents. Therefore, we aimed to systematically review APP prevalence and correlates in the paediatric psychiatric population.

Method

Data sources

An electronic search was carried out on 10 February 2012, updated on 3 July 2012 and 26 January 2013, in PubMed since inception of the data base without language restriction, using the following search terms: (antipsychotic OR antipsychotics) AND (child OR children OR childhood OR adolescent OR adolescents OR adolescence OR pediatric) AND (concomitant OR polypharmacy OR co-prescription OR co-treatment OR combination). Reference lists from retrieved articles were used to further identify additional studies and authors were contacted to provide additional data as necessary.

Study selection

All studies that reported quantitative estimates of APP in antipsychotic-treated children or adolescents were included in the review. We employed a broad working definition of APP as the concurrent use of two or more antipsychotics as reported in each study. This included either at least 1 d of antipsychotic overlap or a required minimal period of combined antipsychotic treatment as per study definition. Whenever possible, studies that combined adult and paediatric populations were included if they allowed separate extraction of data regarding APP in children and adolescents. Similarly, studies that included patients without

antipsychotic treatment in the denominator were included if APP prevalence among antipsychotic-treated patients could be calculated.

Data extraction

Data were extracted by two authors (N.T., J.A.G.) and checked by a third (C.U.C.) using the following categories: author; year of publication of the study; country of origin and country of data collection; number of patients included in the study; setting of the study (in-patient *vs.* out-patient *vs.* mixed); location of the study (urban *vs.* rural); setting in which the study was conducted (teaching hospital *vs.* other); time of data collection. Mean age of the sample and racial information (% white) were also extracted. To further characterize APP, we recorded the definition of polypharmacy from each study, reported APP proportions among subjects receiving antipsychotics and the type of psychiatric co-medications and antipsychotic class combinations [SGA+first-generation antipsychotic (FGA) or (SGA +SGA)].

Statistical method

All analyses were calculated at the study level and not weighted by sample size. Mean and standard deviations for normally distributed data were calculated from the pooled data. Mean age was extracted or calculated for each study and, when data were available (N=11), studies were assigned to one of two groups based on the mean age of the entire study sample, i.e. ≥13.0 (predominantly ‘adolescents’) or <13.0 (predominantly ‘children’). Age groups were assigned in order to compare APP in predominantly pre-pubertal and predominantly post-pubertal patients. To compare potential time trends, studies were categorized by data collection period into studies conducted in the 1990s or 2000s. In three studies where the data collection time spanned both decades, studies were assigned to one of the two decades based on the median time of the data collection period. Pearson’s χ^2 test was used to compare categorical data and t test was used to compare continuous data between the two groups. Correlates of APP were analysed with bivariate analyses, using Pearson’s correlation coefficient. Data were analysed using JMP 5.0.1, 1989–2003, SAS Institute Inc. and STATA version 11 (Stata Corp, USA); all tests were two-sided, and α was set at 0.05.

Results

Search

The literature search identified 1405 articles. Of these, 1358 non-relevant articles were excluded based on the title and the abstract. Of 47 full text articles, 32 were excluded because they either reported on the prevalence of APP in adults, the prevalence of non-APP in children and adolescents or were review articles, yielding 15 studies for the final analyses.

Study characteristics

In the 15 studies (sample size range 68–21 183) APP was examined in a total of 58 041 patients (Table 1). Of the 11 studies with period data, two (18.2%) were conducted entirely in the 1990s, six (54.6%) entirely in the 2000s and three studies (27.3%) included assessments in both the 1990s and 2000s and were assigned to the study decade based on the

median data collection period. There were five studies (*n*=21 581) conducted predominantly in children, seven studies (*n*=746) conducted predominantly in adolescents and three studies with mixed child and adolescent samples without providing a mean age (*n*=35 714). Most studies were performed in urban settings (58.3%), at university/teaching hospitals (58.3%), in out-patients and mixed settings (53.4%) and in the US (80.0%; Table 2).

Ten studies (75.0%) used the broadest definition of APP, requiring ≥1 d of antipsychotic co-treatments and five studies (25.0%) required antipsychotic co-treatment to last for >30 d (Morrato *et al.* 2007), ≥60 d (Constantine *et al.* 2010; dosReis *et al.* 2011; Hong & Bishop, 2010) or ≥90 d (Kogut *et al.* 2005). Moreover, two studies restricted the definition of APP to either a combination of risperidone with another antipsychotic (Simeon *et al.* 2002), or to a combination of FGA+SGA (Wonodi *et al.* 2007).

Studies including samples with a mean age=<13.0 yr ('child' group) did not differ from those with a mean age=≥13.0 ('adolescent' group) regarding any study characteristics besides age, except that six of seven studies (85.7%) in the adolescent groups included only in-patients compared to none in the child studies (*p*=0.0034; Table 2).

Subject characteristics

The mean patient age in the studies was 13.4±1.7 yr (*N*=12), 67.1±10.2% were male (*N*=13) and 56.9±22.4% (*N*=10) were white. The mean patient age in studies assigned to the child group was 11.6±0.9 yr (*N*=5) and 14.6±0.7 yr (*N*=7; *p*=0.0004) in the adolescent group. No significant differences in sex and race were present between the predominantly child and adolescent studies (Table 2).

The most commonly reported diagnoses were attention-deficit hyperactivity disorder (ADHD; 39.1±26.2%), followed by conduct disorder (CD) or oppositional defiant disorder (ODD; 31.5±22.3%). The most common diagnosis in the child studies was ADHD (50.6±25.4%), followed by CD/ODD (39.5±27.5%); whereas the most common diagnoses in the adolescent studies were schizophrenia-spectrum disorders (28.6±23.8), anxiety disorders (26.9±14.9) and bipolar-spectrum disorders (26.6±17.2), followed closely by CD/ODD (25.8±17.7; Table 2).

Psychotropic medication prescribing patterns

Among the study samples, the most commonly prescribed antipsychotics were SGAs (77.9±27.4%). The FGA proportion was 14.5±17.2% (*N*=7) in the entire sample and 3.6±2.9% (*N*=2) in the child group *vs.* 18.9±19.0% (*N*=5) in the adolescent group (*p*=0.33; Table 3). While the prevalence of SGA prescribing did not differ in studies conducted in the 1990s (77.5±23.3%) or 2000s (76.8±36.3%, *p*=0.96), FGAs accounted for a smaller percentage in the studies conducted in the 2000s than in the earlier period (5.4±5.2% *vs.* 37.2±15.3%, *p*=0.0060). The mean proportion of subjects receiving clozapine (0.6±0.8%) and long-acting, injectable antipsychotics (0.1%) was very low (Table 3).

The mean reported prevalence of APP was 9.6±7.2%. This estimate was consistent (*p*=0.89) across studies with a broad APP definition [i.e. ≥1 d of antipsychotic co-treatment (*N*=10): 9.8±7.8%] and those with a more conservative definition [i.e. requiring a minimum of 1–3

months of combined antipsychotic use (*N*=5): (9.2±6.5%)]. The APP prevalence was 7.2±4.7% in studies conducted in the 1990s (*N*=5) and 9.8±7.8% in those conducted in the 2000s (*N*=9; *p*=0.51).

The most common antipsychotic class combination was FGA+SGA (70.9±44.1%) followed by SGA+SGA (30.2±45.5%). FGA+FGA combinations were absent in the nine studies with data. Across the two decades, the proportion of FGA+SGA combinations (100±0% *vs.* 53.0±54.5%, *p*=0.14) did not differ significantly.

Antidepressants (38.1±18.3%) and mood stabilizers (37.4±24.8%) were the most commonly prescribed co-medications, followed by psychostimulants (31.5±26.0%), anxiolytics/hypnotics (17.0±18.9%) and anticholinergics (13.8±9.5%) (Table 3).

Psychotropic medication prescribing characteristics by predominant age group (children *vs.* adolescents)

The mean APP prevalence was numerically lower in children (5.9±4.5%) than in adolescents (12.0±7.9%, *p*=0.15; Table 3). The mean APP prevalence for the predominantly child sample was 6.1±4.6% (*N*=2) in the 1990s and 5.9±5.5% (*N*=3) in the 2000s (*p*=0.97). By contrast, the mean APP prevalence in predominantly adolescent samples rose non-significantly from 7.9±5.6% (*N*=3) in the 1990s to 15.1±8.6% (*N*=4) in the 2000s (*p*=0.27).

Similarly, statistically non-significant differences were observed between predominantly child and adolescent samples regarding antipsychotic class combinations. FGA+SGA combinations were commonly prescribed in both child and adolescent samples (100% *vs.* 62.4±51.7%, *p*=0.27), whereas SGA+SGA combinations were not described in child, but only in adolescent samples (0.0±0.0% *vs.* 37.6±51.7%, *p*=0.27; Table 3).

In the child samples, stimulants were most commonly co-prescribed with antipsychotics (51.9±25%), significantly more than in adolescent samples (14.6±9.1%, *p*=0.0076), followed by antidepressants (47.8±22.0%). By contrast, in the adolescent samples, mood stabilizers were the most frequent co-medication class (40.8±21.7%), also followed by antidepressants (32.6±14.7%; Table 3).

Correlates of APP

Bivariate ecological comparisons at the study level revealed a significant positive correlation between increasing APP prevalence and larger proportions of subjects with a diagnosis of bipolar- or schizophrenia-spectrum disorders (r^2=0.08, *p*=0.019), co-treatment with anxiolytics/hypnotics (r^2=0.08, *p*=0.869), as well as SGA+SGA combinations (r^2=0.746, *p*=0.0027). Correspondingly, FGA+SGA combinations showed a significant negative correlation with APP prevalence (r^2=0.738, *p*=0.0030). No other variables were significantly correlated with APP (Table 4).

Discussion

In this systematic review of APP patterns in youth, the average APP prevalence in child and adolescent studies was 9.6±7.2%. The prevalence among child studies (5.9±4.5%) was

numerically lower than among adolescent studies (12.0±7.9%), but the small number of studies limited formal inferences. The average APP prevalence estimates in youth studies in the 1990s (7.2%) and 2000s (9.8%) were lower than the respective estimates of 22.0 and 19.2% in these decades in a systematic review of APP prevalence in adults (Gallego *et al.* 2012a). This lower APP prevalence in youth is consistent with a much lower prevalence of psychotic disorders in antipsychotic-treated paediatric studies (22.27%) compared to adult studies (82.9%) and a significant positive correlation in the paediatric samples between APP and a diagnosis of a bipolar- or schizophrenia-spectrum disorder. In a meta-regression of 147 studies and 1 418 163 adult patients, APP was also associated with a schizophrenia diagnosis, in addition to in-patient status and FGA use (R^2=0.44, p<0.0001; Gallego *et al.* 2012a). While the APP prevalence remained stable across the two decades of investigation in the child studies (i.e. 6.1 and 5.9%), the APP prevalence in predominantly adolescent studies almost doubled from 7.9% in the 1990s to 15.1% in the 2000s. This is a potentially concerning trend that needs to be examined further, given that our findings were based on a relatively small number of studies.

In recent years, the perceived efficacy, safety, ease of use and tolerability of SGAs has led to their increasing utilization in the treatment of non-psychotic symptoms and disorders in children and adolescents (Olfson *et al.* 2006, 2012). In recent years, five SGAs (aripiprazole, olanzapine, paliperidone, quetiapine, risperidone) have received FDA approval for use in children and adolescents with schizophrenia, four have been approved for paediatric bipolar mania and two for use in autistic youth with significant irritability (Correll *et al.* 2011). In the studies reporting on APP, most patients were prescribed SGAs (77.9%). Prescription rates for FGAs were far lower (14.5%) in the overall sample, in predominantly adolescent samples (18.9%) and, particularly, in predominantly child samples (3.6%). However, FGAs were prescribed significantly more commonly in the one study reporting on antipsychotic class prescribing in the 1990s (37.2%) than in studies conducted in the 2000s (5.4%). This strong shift to SGAs in youth in the 2000s is in contrast to FGA prescription rates reported in adults in the 1990s (53.0%) and 2000s (40.5%; Gallego *et al.* 2012a). Similar results were found in a recent study from the US, which analysed out-patient visits to physicians in office-based practices from the 1993–2009 National Ambulatory Medical Care Surveys (*N*=484 889). In this study, FGAs also represented a greater proportion of adult (11.9%) than adolescent (1.8%) or child (1.3%) antipsychotic medications (Olfson *et al.* 2012). Thus, in youth, clinicians use FGAs much more sparingly, which is likely related to the high risk for acute extra pyramidal side-effects (EPS; Correll, 2008) and the significantly lower long-term risk of SGAs for tardive dyskinesia in adults (Correll *et al.* 2004) and youth (Correll *et al.* 2007).

Similar to adult studies (Kreyenbuhl *et al.* 2007; McCue *et al.* 2003), we found that the most common antipsychotic class combination consisted of FGA+SGA (70.9%). Subgroup analyses revealed that all three child studies with data on antipsychotic class combinations reported only FGA+SGA combinations. This combination was also more commonly prescribed in adolescent studies (62.4%), but 37.6% of combinations included SGAs only. This overall finding is in contrast to a previous study, in which 89% of the days of APP in the 6–12 yr age group and 73% of the days of APP in adolescents involved combinations of

SGAs (Constantine *et al.* 2010). However, this study reported data from 2002 to 2007, when SGAs were generally more widely prescribed.

Although APP consisted mostly of SGA+FGA combinations, higher use of SGA+SGA and lower proportions of FGA+SGA combinations were associated with increased overall APP prevalence. This is consistent with the aforementioned lower EPS rates with SGAs than FGAs, which are therefore more readily combined, especially in children and adolescents who are particularly sensitive to EPS (Correll, 2008). Nevertheless, the extent of FGA+SGA combinations as well as the lack of difference between APP prevalence in studies using a broad definition of APP (i.e. at least 1 d of antipsychotic co-treatment) compared to studies that required at least 30, 60 or 90 d of combined antipsychotic use suggests substantial proportions of deliberate antipsychotic co-treatment, rather than overlapping antipsychotic use during switching. In adult studies, however, definitions of APP requiring longer periods of antipsychotic co-prescribing were associated with lower APP prevalence (Gallego *et al.* 2012a). Future studies should report on APP using varying thresholds of required APP duration to determine the true prevalence of long-term APP.

Although a strong association between schizophrenia and APP has been demonstrated in adults (Biancosino *et al.* 2006; Castberg & Spigset 2008; Fourrier *et al.* 2000; Morrato *et al.* 2007) and in two paediatric studies (Constantine *et al.* 2010; dosReis *et al.* 2011), schizophrenia-spectrum disorders were not correlated with APP in the overall reviewed database. This may be a problem of sample size or related to the different indications of use of APP in younger populations. One study of 16 969 foster youth with mean age of 12.8 yr included in our review (dosReis *et al.* 2011) showed that youngsters were more likely to be prescribed concomitant antipsychotics if they had a diagnosis of CD (odds ratio 1.43, $p<0.001$). In our overall analyses, however, we did not find a significant correlation between individual diagnoses and APP. Nevertheless, the high prescribing rates of antipsychotics for youth with ODD and CD, or even ADHD (Olfson *et al.* 2012), are clearly of concern, as no FDA approval exists and other, non-pharmacological treatments should be used first (Scotto-Rosato *et al.* 2012). Combining bipolar-with schizophrenia-spectrum disorders revealed a correlation with APP ($p=0.019$). Unlike adult studies (Correll & Gallego, 2012), we found no significant correlation between APP and male sex, use of clozapine or long-acting injectables, prescription of any other co-medications, including anticholinergics or lower antidepressant rates in the paediatric samples included in this review. However, there was a significant correlation between greater use of anxiolytics/hypnotics and APP in youth ($p=0.0067$). To date, it is unclear what this correlation is due to, but it is possible that benzodiazepines as well as a second antipsychotic are used in an attempt at targeting agitation and aggression in seriously ill youth.

The results of this study have to be interpreted within its limitations. First, the number of studies reporting on APP in youth was limited and study sizes and clinical settings varied widely. Second, APP definitions varied between studies. Two studies limited the APP definition to specific agents (risperidone+AP and FGA+SGA, respectively), likely resulting in an underestimation of the true APP prevalence. In addition, the broad definition of APP in 10 of the 15 studies that included at least APP day does not permit distinguishing short-term overlap of antipsychotic treatment during cross-titration from intended longer-term APP.

However, APP consisted predominantly of FGA+SGA combinations. Since FGA monotherapy has become rather uncommon in youth, the FGA-SGA combination is most likely part of longer-term APP. The fact that the proportion of FGA-SGA combination did not differ between the 1990s, where switching from FGAs to SGAs would have been more common, strengthens the argument that FGA+SGA combinations may in fact be part of intended longer-term APP use. Third, we did not have data on prior treatment attempts and failures or other data that could have provided clues to the reasons for, and the risks and benefits of, the implemented APP. In this context, the limited data did not allow us to confirm clozapine that was prescribed to only 0.6% of youth across five studies with data was underutilized in patients with schizophrenia-spectrum disorders. Similarly, we could not assess if APP was used instead of more appropriate and evidence-based use clozapine in youth with refractory schizophrenia (Schimmelmann *et al.* 2013), as has been suggested in adults (Nielsen *et al.* 2010a,b). Fourth, as with any review and pooled analysis, combining data from studies that were conducted using different methodologies, at different time-points, in different countries and patient populations makes a direct comparison of studies difficult. Finally, all comparisons were ecological on the level of study data and did not allow inferences on the level of individual patients. Nevertheless, to our knowledge, this is the first review that focuses on the prevalence and correlates of APP in children and adolescents and our analyses provide initial data that should be followed up further.

In summary, this review suggests that APP is not uncommon in children and adolescents. The average APP prevalence from 15 studies suggests that about one in 10–11 youth who receive an antipsychotic medication receive APP. This proportion was observed in studies using broad and more restricted definitions of APP. In adolescent samples studied in the 2000s, the mean prevalence was even higher, implicating one in eight youth. This practice is of concern, as its benefits are unclear and its long-term safety is not well established. Further research is needed to better understand the reasons for and correlates of short-term and sustained APP in youth and to identify its potential risk and benefits in the vulnerable paediatric population, especially for young people with non-psychotic disorders.

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Table 1

Study design and patient population characteristics

Author, yr (continent and study period)	*N*	Age (yr)	Male (%)	White (%)	Setting IP, OP, M	Definition of APP	APP (%)	SCZ-spectrum (%)	ODD or CD (%)	ADHD (%)	Depression (%)	Anxiety (%)	Bipolar spectrum (%)
Studies with a mean age ≤12 yr (Child studies)													
dosReis ’11 (US, 2003)	16969	12.8	69.8	67.3	M	≥2 APs >30 d	6.5	19.9	53.1	53.3	33.8	12.9	20.8
Jerrell & McIntyre ’08 (US, 1996–2005)	4140	10.4	68.2	41.6	M	≥2 SGAs	11	36.4	71.7	78.7	–	–	–
Wonodi ’07 (US, NR)	118	11.9	77.1	–	M	FGA+SGA	9.3	19	–	64	–	–	–
Dean ’06 (Australia, 2002–2003)	248	12	50	–	M	≥2 APs	0.08	2.8	14.5	10.8	–	23.3	–
Simeon ’02 (US, 1994–1999)	106	11	76.4	–	OP	Ris+AP	2.8	3.8	18.8	46.2	3.7	7.5	–
Studies with a mean age ≥13 yr (Adolescent studies)													
Hong ’10 (US, ≥2005–2008)	152	14.5	49	18	OP	≥2 APs >60 d	9	13.2	–	23	17.1	31.5	43.4
Patel ’07 (US, 2004–2005)	95	14	57	60	IP	≥2 APs	27	14	46	–	26	39	52
Castro-Fornieles ’08 (Spain, NR)	110	15.5	67.3	85.5	M	≥2 APs	15.5	77.3	–	–	11.8	–	10.9
Laita ’07 (Spain, 2003–2005)	126	15.6	61.9	88.1	IP	≥2 APs	8.7	39.6	18.2	3.2	–	–	18.2
Kelly ’04 (US, 1997–2000)	68	14.9	76	40.5	IP	≥2 APs	2.9	16.1	13.2	–	25	–	23.5
Pappadopulus ’02 (US, NR)	100	14.3	69	46	IP	≥2 APs	14	11.3	–	–	24	10.3	11.8
Connor ’01 (US, 1993–1999)	95	13.7	82	75.8	IP	≥2 APs	6.9	28.4	–	–	–	–	–
Studies with missing data for mean age													
Constantine ’10 (US, 2002–2007)	23 183	≤18	68	46	OP	≥2 APs >60 d	7.5	7.4	16.6	33.7	4.8	6.6	15.9
Morrato ’07 (US, 1998–2003)	11 977	≤17	–	–	–	≥2 APs ≥60 d	3.3	–	–	–	–	–	–
Kogut 2005 (US, NR)	554	≤18	–	–	–	≥2 APs ≥90 d	4.5	–	–	–	–	–	–
Total: *N*=15	58 041	13.4±1.7	67.1±10.2	56.9±22.4	I*P*=5; M=5; O*P*=3	≥2 APs = 8; Ris +AP=1; FGA +SGA; ≥2 APs >30 d=1	9.6±7.2	22.2±20.1	31.5±22.3	39.1±26.2	18.3±10.8	19.2±11.3	24.6±15.1

Author, yr (continent and study period)	*N*	Age (yr)	Male (%)	White (%)	Setting IP, OP, M	Definition of APP	APP (%)	SCZ-spectrum (%)	ODD or CD (%)	ADHD (%)	Depression (%)	Anxiety (%)	Bipolar spectrum (%)
						≥2AP ≥60 d=3; ≥2 APs ≥90 d=1							

IP, In-patient; OP, out-patient; M, mixed; APP, antipsychotic polypharmacy; SCZ, schizophrenia; ODD, oppositional defiant disorder; CD, conduct disorder; ADHD, attention deficit-hyperactive disorder; NR, not reported; SGA, second-generation antipsychotic; FGA, first-generation antipsychotic; AP, antipsychotic; Ris, risperidone.

Table 2

Study and patient characteristics

	Total sample[a] ***N*=58 041**	**Predominantly child studies**[b] ***n* = 21 581**	**Predominantly adolescent studies**[c] ***N*=746**	***p* value**
Study characteristics				
Number of studies	*15* [a]	*5*	*7*	
Study period (*N*,%)				0.92
Median <2000	5 (35.7%)	2 (40.0%)	3 (42.7%)	
Median ≥2000	9 (64.3%)	3 (60.0%)	4 (57.1%)	
Location (*N*,%)				0.49
Urban	7 (58.3%)	3 (60.0%)	4 (80.0%)	
Mixed (urban and rural)	5 (41.7%)	2 (40.0%)	1 (20.0%)	
Institution type (*N*,%)				0.34
University-teaching institutions	7 (58.3%)	2 (50.0%)	4 (80.0%)	
Non-university/mixed institutions	5 (41.7%)	2 (50.0%)	1 (20.0%)	
Setting (*N*,%)	(13)	(5)	(7)	**0.0034**
In-patient	6 (46.2%)	0 (0%)	6 (85.7%)	
Out-patient and mixed[d]	7 (53.4%)	5 (100.0%)	1 (14.3%)	
Country (*N*,%)	(15)	(5)	(7)	0.24
United States	12 (80.0%)	4 (80%)	5 (71.5%)	
Europe	2 (13.3%)	0 (0%)	2 (28.6%)	
Australia	1 (6.7%)	1 (20%)	0 (0%)	
Patient characteristics				
Demographics				
Age (mean, S.D.)	13.4±1.7 (12)	11.6±0.9 (5)	14.6±0.7 (7)	**0.0004**
White (*N*,%)	56.9±22.4 (10)	54.5±18.2 (2)	59.1±25.9 (7)	0.82
Male (*N*,%)	67.1±10.2 (13)	68.3±11.0 (5)	66.0±11.2 (7)	0.73
Diagnosis (*N*,%)				
ADHD	39.1±26.2 (8)	50.6±25.4 (5)	13.1±14.0 (2)	0.12
CD or ODD	31.5±22.3 (8)	39.5±27.5 (4)	25.8±17.7 (3)	0.49
Bipolar spectrum disorders	24.6±15.1 (8)	20.8 (1)	26.6±17.2 (6)	0.77
SCZ-spectrum disorders	22.2±20.1 (13)	16.4±13.8 (5)	28.6±23.8 (7)	0.33
Anxiety disorders/depressive disorders	18.7±12.7 (7)	14.6±8.0 (3)	26.9±14.9 (3)	0.27
Pervasive developmental disorders	18.3±10.8 8)	18.8±21.3 (2)	20.8±6.15)	0.83
	14.2±10.2 (7)	16.7±10.4 (3)	12.3±11.2 (4)	0.62

ADHD, Attention deficit-hyperactivity disorder; CD, conduct disorder; ODD, oppositional defiant disorder; SCZ, schizophrenia.

Values shown in bold indicate significant *p* values.

[a] Not all studies contributed data to all categories and the total number of studies is larger than the sum of child and adolescent studies, as data for mean age were not available in two studies.

[b] Studies in which the mean participant age was <13.0 yr.

[c] Studies in which the mean participant age was ≥13.0 yr.

[d] Four studies contained mixed samples, predominantly consisting of out-patients, and 3 studies contained exclusively outpatients; Number of studies contributing data is shown in parentheses.

Table 3

Psychotropic medication prescribing practices in the total sample and in subsamples consisting predominantly of children *vs.* adolescents

Treatment characteristics	Total no. of studies with data[a]	Total sample *N*=15[a]	Predominantly child studies[b] *n*=21 581	Predominantly adolescent studies[c] *N*=636	*p* value[d]
Antipsychotics					
1 antipsychotic	13	81.4±14.1	75.8±16.5 (4)	80.9±13.5 (7)	0.59
2 antipsychotics	10	11.6±11.5	4.5±1.6 (3)	16.4±13.1 (6)	0.17
3 or more antipsychotics	8	0.01±0.01	0.01±0.02 (3)	0.0±0.0 (5)	0.22
APP (≥2 antipsychotics)[e]	15	9.6±7.2	5.9±4.5 (5)	12.0±7.9 (7)	0.15
FGA	7	14.5±17.2	3.6±2.9 (2)	18.9±19.0 (5)	0.33
SGA	11	77.9±27.4	70.0±40.7 (4)	82.4±18.9(7)	0.50
Clozapine	5	0.6±0.8	0.4 (1)	0.7±1.2 (3)	0.85
Long-acting injectable antipsychotics	1	0.1	0.1 (1)	− (0)	NA
APP (≥2 antipsychotics) pattern					
FGA+FGA	9	0.0±0.0	0.0±0.0 (3)	0.0±0.0 (5)	NA
SGA+SGA	9	30.2±45.5	0.0±0.0 (3)	37.6±51.7 (5)	0.27
FGA+SGA	9	70.9±44.1	100±0.0 (3)	62.4±51.7 (5)	0.27
Co-medications					
Antidepressants	11	38.1±18.3	47.8±22.0 (4)	32.6±14.7 (7)	0.20
Mood stabilizers[f]	12	37.4±24.8	32.7±30.7 (5)	40.8±21.7 (7)	0.60
Stimulants	11	31.5±26.0	51.9±25.0 (5)	14.6±9.1 (6)	**0.0076**
Anxiolytics/hypnotics	6	17.0±18.9	3.4±3.3(2)	23.8±20.2 4)	0.25
Anticholinergics	6	13.8±9.5	1.0 (1)	16.4±8.0 (5)	0.15

APP, Antipsychotic polypharmacy; FGA, first-generation antipsychotic; SGA, second-generation antipsychotic.

Values shown in bold indicate significant *p* values.

[a] Not all studies contributed data to all categories and the total number of studies is larger than the sum of child and adolescent studies, as data for mean age were not available in two studies.

[b] Studies in which the mean participant age was <13.0 yr.

[c] Studies in which the mean participant age was ≥13.0 yr.

[d] *t* test.

[e] The APP prevalence is not identical to the sum of patients taking 2 or ≥3 antipsychotics, as not all studies reporting on APP specified the exact number of antipsychotics prescribed.

[f] The terms ‘mood stabilizers’ consists of ‘mood stabilizers’ and ‘anticonvulsants’ plus ‘lithium’ as reported in the publications.

Table 4

Correlates of antipsychotic polypharmacy

Variables	No. of studies	r^2	*p* value
Demographics			
Mean age	12	0.090	0.34
% White	10	0.022	0.68
% Male	13	0.038*	0.52
Diagnoses			
% Psychotic disorders	13	0.10	0.29
% Bipolar spectrum disorders	8	0.225	0.24
% Bipolar or schizophrenia spectrum disorders	**13**	**0.408**	**0.019**
% Depressive disorders	8	0.070	0.53
% Anxiety disorders	7	0.328	0.18
% ADHD	8	0.175	0.30
% Pervasive developmental disorders	7	0.116	0.45
% ODD/Conduct disorders	8	0.258	0.20
Treatment			
% FGA	7	0.001	0.94
% SGA	11	0.133	0.27
% Clozapine	5	0.001	0.97
% Decanoate preparations	1	NA	NA
% Mood stabilizers	12	0.014	0.72
% Anxiolytics/hypnotics	**6**	**0.869**	**0.0067**
% Antidepressants	11	0.001	0.94
% Stimulants	11	0.002	0.89
% Anticholinergics	6	0.005	0.90
% SGA+SGA	**9**	**0.746**	**0.0027**
% FGA+SGA	**9**	**0.738** *	**0.0030**

ADHD, Attention deficit-hyperactivity disorder; FGA, first-generation antipsychotic; ODD, oppositional defiant disorder; SGA, second-generation antipsychotic.

Values shown in bold indicate significant *p* values.

* Negative correlation.