Best Clinical Practices in Child and Adolescent Psychiatry

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Discussion of off-label or investigational use:

Yes _X_ No __

Overview

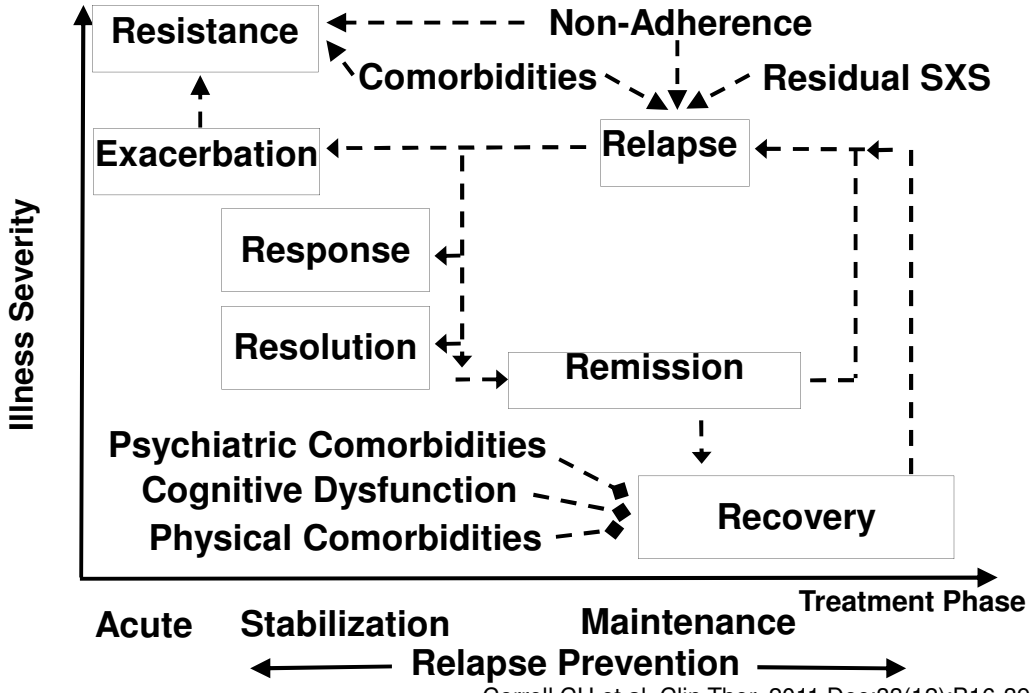
- General Principles of Best Practices
  - Measurement Based Approaches
  - Evidence Based Decisions
  - Individualization of Care
  - Documentation of Rationale
  - Quality Indicators
- Example of Polypharmacy
  - Reasons and Concerns
  - Evidence Base in Youth
  - Randomized Controlled Evidence in Adults
- Cardiometabolic Risk Monitoring and Management
- Conclusions

General Principles

Best Clinical Practices

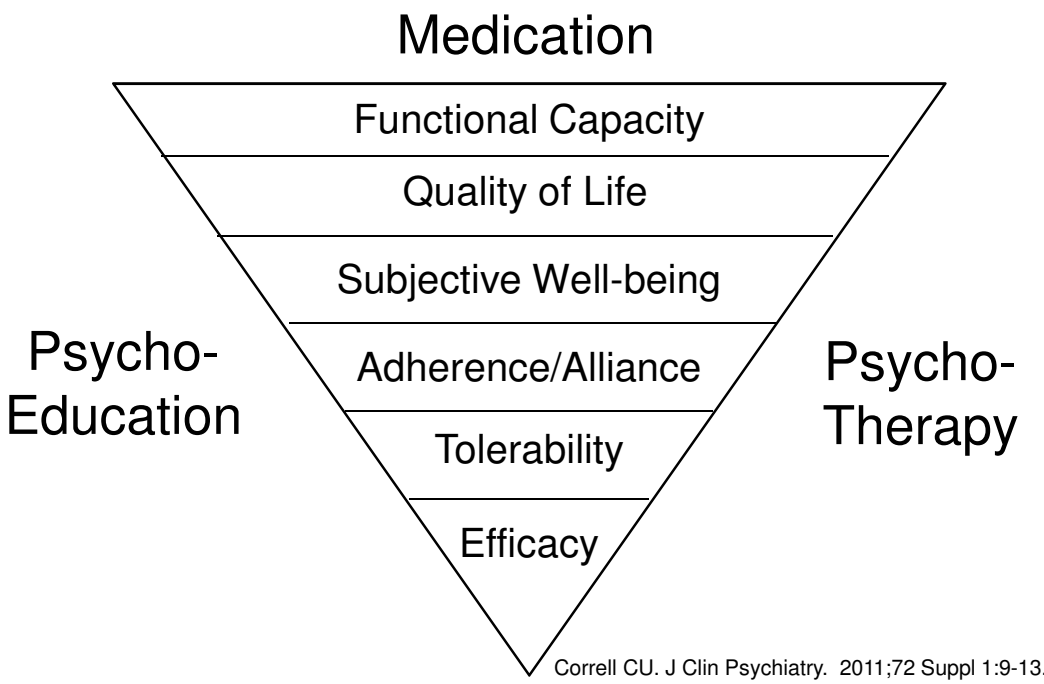
- Measurement Based Approaches
- Evidence Based Decisions
- Individualization of Care
- Multipronged, multi-team member approach
- Documentation of Rationale
- Quality Indicators

Treatment Goals and Threats



Correll CU et al. Clin Ther. 2011 Dec;33(12):B16-39.

The Effectiveness Pyramid



Correll CU. J Clin Psychiatry. 2011;72 Suppl 1:9-13.

Management Challenges

Mental d/o's are among the 10 most disabling conditions

The pathophysiology and response predictors are unknown

Youth undergo enormous biopsychosocial changes

Physical Comorbidities1	• **Cardiovascular disease1** • **Diabetes1** • **Obesity1**
Psychiatric comorbidities2	• **Access to services** • **Substance abuse** • **Anxiety disorder**
Functioning3	• **Impaired social and family functioning2** • **Sustained impairments in cognitive functioning2**
Residual symptoms4	• **Predictive of poor outcomes3**

1. Kupfer DJ. JAMA 2005;293:2528-30; 2 Angst et al. Arch Gen Psychiatry. 2011; in press; 3. Bowden. J Clin Psychiatry. 2009;70:e32; 4. Weinstock & Miller. Compr Psychiatry. 2010;51497–503.

Selected Risk and Protective Factors for Mental Health of Children and Adolescents

	Risk factors	Protective factors
Biological		
	Exposure to toxins (eg, tobacco, alcohol) in pregnancy Genetic tendency to psychiatric disorder Head trauma Hypoxia at birth and other birth complications HIV infection Malnutrition Substance abuse Other illnesses	Age-appropriate physical development Good physical health Good intellectual functioning
Psychological		
	Learning disorders Maladaptive personality traits Sexual, physical, emotional abuse and neglect Difficult temperament	Ability to learn from experiences Good self-esteem High level of problem-solving ability Social skills
Social		
Family	Inconsistent care-giving Family conflict Poor family discipline Poor family management Death of a family member	Family attachment Opportunities for positive involvement in family Rewards for involvement in family
School	Academic failure Failure of schools to provide appropriate environment to support attendance and learning Inadequate or inappropriate provision of education Bullying	Opportunities for involvement in school life Positive reinforcement from academic achievement Identity with school or need for educational attainment
Community	Transitions (eg, urbanisation) Community disorganisation Discrimination and marginalisation Exposure to violence	Connectedness to community Opportunities for leisure Positive cultural experiences Positive role models Rewards for community involvement Connection with community organisations

Patel V et al. Lancet. 2007 Apr 14;369(9569):1302-13.

Clinical Decisions

- How much improvement is enough?
- When do we change treatments?
- When do we change them again?
- When do adverse effects determine changes in treatment?
- Can locus of care be changed?

Correll CU et al. Clin Ther. 2011 Dec;33(12):B16-39.

How should we define and measure response?

- Change score
- Percent improvement
- Final score
- Clinical Global Impression

Correll CU et al. Clin Ther. 2011 Dec;33(12):B16-39.

The Value of Measurement

- Contribution to diagnostic process
- Establishing baseline severity
- Providing targets and treatment goals
- Evaluating the efficacy of treatment
- Evaluating tolerability and adverse effects
- Influencing level of care
- Medical record documentation

Correll CU et al. Clin Ther. 2011 Dec;33(12):B16-39.

Obstacles to Measurement

- Inadequate appreciation of benefit
- Perceived value of global judgment
- Time constraints
- Lack of appropriate instruments
- Inadequate training
- Reimbursement concerns

Correll CU et al. Clin Ther. 2011 Dec;33(12):B16-39.

Guidelines

- Guidelines are recommendations for a standardized treatment approach
- Guidelines are based on evidence that is derived from mean scores on a primary symptom scale in patients agreeing to be part of randomized controlled trials
- Individualization of clinical care is paramount to achieve best outcomes for specific patients

Opportunities for Individualized Care

Illness Profile	Patient Profile	Medication Profile
History of illness onset and course	Vulnerability to adverse effects	Pharmacodynamics
Presenting signs and symptoms	Tolerance of adverse effects	Pharmacokinetics
Past treatment response	Insight and attitude toward illness	Co-Treatments ((DDI)
	Preference for treatment approaches	Efficacy and Effectiveness
	Comorbid medical conditions	Tolerability (short- and long-term)
	Comorbid psychiatric conditions	Delivery methods/ formulations available
	Comorbid substance abuse	Need for monitoring
	Social support network	Availability/cost

Adapted from: Kane JM and Correll CU. Dialogues Clin Neurosci. 2010;12(3):345-57.

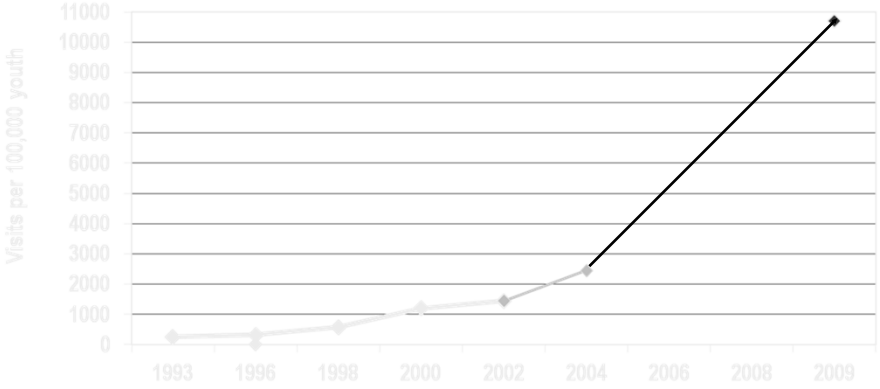
Quality Indicators

Qualitative and Quantitative Documentation of:

- Target Problems
- Treatment Plan
- Matching of Interventions to Specific Problems
- Rationale (Reasons, Evidence, Alternatives)
- Consent
- Time Frame + Indicators of Success / Failure
- Outcome(s) (Desired and Undesired)
- Rationale for Continuation or Changes
- Procedures for Guideline Inconsistent Practice

Antipsychotics

Atypical Antipsychotic Use Increasing Dramatically in Youth



1993-2002: Olfson M et al. Arch Gen Psychiatry. 2006 Jun;63:679-85;
2003-2004 Aparasu R & Bhatara V. Curr Med Res Opin. 2007 Jan;23(1):49-56;
1993-2009 Olfson M et al. Arch Gen Psychiatry. 2012 Dec;69(12):1247-56

- 2002: ~10% of mental health visits involved SGA treatment
- 2005-2009: 31% of psychiatrists visits involved antipsychotic treatment
- 2005-2009: DBDs most common diagnoses in child 63% and adolescent (34%) visits

Curr Psychiatry Rep (2013) 15:382

Pharmacoepidemiology of Antipsychotic Use in Youth with ADHD: Trends and Clinical Implications

Michael L. Birnbaum · Ema Saito · Tobias Gerhard · Almut Winterstein · Mark Olfson · John M. Kane · Christoph U. Correll

Abstract Although concern has been raised about antipsychotic prescribing to youth with attention-deficit/hyperactivity disorder (ADHD), the available database is limited to individual studies. Therefore, in order to provide a synthesis of prevalence and time trends, we conducted a systematic review and pooled analysis of pharmaco-epidemiologic data on antipsychotic use in ADHD youth. Of 1806 hits, 21 studies (N) were retained that reported analyzable data for three separate populations: 1) antipsychotic-treated youth (N=15, n=341,586); 2) ADHD youth (N=9, n=6,192,368), and 3) general population youth (N=5, n=14,284,916). Altogether, 30.5±18.5 % of antipsychotic-treated youth had ADHD. In longitudinal studies, this percentage increased over time (1998–2007) from 21.7±7.1 % to 27.7±7.7 %, ratio=1.3±0.4. Furthermore, 11.5±17.5 % of ADHD youth received antipsychotics. In longitudinal studies, this percentage also increased (1998–2006) from 5.5±2.6 % to 11.4±6.7 %, ratio=2.1±0.6. Finally, 0.12±0.07 % of youth in the general population were diagnosed with ADHD and received antipsychotics. Again, in longitudinal studies, this percentage increased over time (1993–2007): 0.13±0.09 % to 0.44±0.49 %, ratio=3.1±2.2. Taken together, these data indicate that antipsychotics are used by a clinically relevant and increasing number of youth with ADHD. Reasons for and risk/benefit ratios of this practice with little evidence base require further investigation.

Keywords Attention-deficit/hyperactivity disorder · ADHD · Antipsychotics · Prescribing · Trends · Correlates · Pharmacoepidemiology · Psychiatry

Introduction

Over the past two decades psychotropic medication prescriptions for children and adolescents in the United States have grown considerably [1••, 2]. Although medication use has increased for all psychotropic medication classes,

Polypharmacy

Management of Treatment Resistant Patients

1. Reassess diagnosis, r/o medical or substance related condition
2. Identify comorbidities and optimize their management
3. Review nature and effectiveness of current and past treatments
4. Assess for side effects potentially contributing to refractoriness
5. R/o potentially interfering drug-drug interactions
6. Check and address reasons for non-adherence
7. Optimize non-pharmacologic treatments
8. Continue treatment and wait for a potentially delayed response

Kane JM, Kishimoto T, Correll CU. UpToDate - In press.

Reasons for Polypharmacy

- Cross-titration (active or aborted)
- Enhance effect
- Speed-up effect
- Different target symptom
- Different symptom domain
- Reduce adverse effects
- Different route of administration
- Different pharmacological mechanism
- Poor communication between services
- Patient's/family's choice / pressure
- Prescriber habit
- Marketing

Correll CU. CNS Spectr. 2010 Apr;15(4 Suppl 6):8-11.

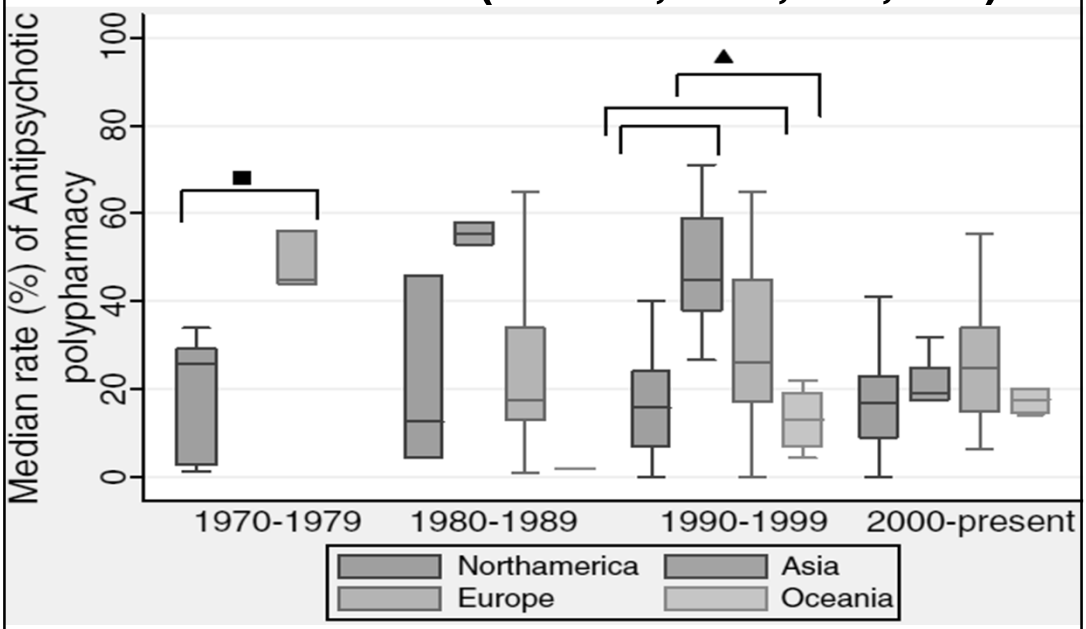
Concerns about Polypharmacy

- Higher than necessary total dosage
- Increased acute side effects
- Increased long term side effects
- Loss of “atypicality”
- Drug-drug interactions
- ? Increased mortality
- Increased risk of non-adherence
- Difficulty determining cause and effect
- Cost
- Lack of evidence base

Correll CU. CNS Spectr. 2010 Apr;15(4 Suppl 6):8-11.

Frequency of Antipsychotic Polypharmacy

Antipsychotic Polypharmacy in SCZ from 1970-2009 (N=147, n=1,418,163)



Gallego JA et al. Schizophr Res. 2012 Jun;138(1):18-28.

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doi:10.1017/S1461145712001320

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

Nitin Toteja[1], Juan A. Gallego[1,2], Ema Saito[1], Tobias Gerhard[3,4], Almut Winterstein[5], Mark Olfson[6] and Christoph U. Correll[1,2,7,8]

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 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.

Correlates of Antipsychotic Polypharmacy

Correlates of AP Polypharmacy in SCZ: Patient and Illness Characteristics

PATIENT

- **Younger age (but adolescents > children)**
- **Male sex**
- **White/non-Latino; African-American race ?**
- **Unmarried**

ILLNESS

- **Earlier illness onset, longer Illness duration**
- **Greater illness acuity or severity, less improvement**
- **Treatment resistance**
- **Schizophrenia/schizoaffective disorder/ Psychotic disorder**
- **More negative symptoms**
- **History of violence**
- **Less illness insight**
- **More psychiatric comorbidity**

Correll CU and Gallego JA. Psychiatr Clin N Am. 2012 Sep;35(3):661-681.

Correlates of AP Polypharmacy in SCZ: Treatment Characteristics

- Involuntary treatment
- Hospitalization, longer inpatient stay

- Longer treatment, multiple switches

- Antipsychotic polypharmacy at baseline

- Inherited by other MD
- Partial adherence
- Higher total dose
- Treatment with quetiapine
- Treatment with typical neuroleptics

- Treatment with depot neuroleptics

- Treatment with clozapine (+/-)
- Less use of olanzapine (+/-)
- Treatment with anticholinergics
- Treatment with mood stabilizers

Correll CU and Gallego JA. Psychiatr Clin N Am. 2012 Sep;35(3):661-681.

Correlates of AP Polypharmacy in SCZ: Provider and Other Characteristics

PROVIDER

- Region/country/prescriber
- Metropolitan area
- Treatment by same doctor for >2 years

- Non-teaching hospital, less research involvement

- Less attendance at local CME activities

- More senior staff vs. trainees
- Specific APP preference
- Greater reliance on prior provider's APP recommendation

- Attendance at educational programs sponsored by a pharmaceutical company

- Time pressure, work load

Correll CU and Gallego JA. Psychiatr Clin N Am. 2012 Sep;35(3):661-681.

Schizophrenia Research 131 (2011) 58–62

Antipsychotic polypharmacy: A survey study of prescriber attitudes, knowledge and behavior

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ABSTRACT

Objective: Although common in psychiatric practice, reasons for antipsychotic polypharmacy (APP) have remained unclear.
Methods: Single-site, semi-structured interview study of prescribers at a psychiatric teaching hospital inquiring about APP attitudes and behaviors, including frequency, preferred combinations, rationale and concerns.
Results: Forty-four prescribers reported using APP in 17.0±10.0% of antipsychotic-treated patients. Although clinicians themselves initiated APP in only 23.3±27.0% of cases, they did not attempt conversion to antipsychotic monotherapy in 40.9±37.7%, despite reported successful conversion in 28.0±30.8% of cases. The following reasons justified most APP (0–10): cross-titration (9.2±1.4), failed clozapine trial (8.2±2.2), randomized controlled evidence (8.0±2.0), and clozapine intolerance (7.7±2.6). Prescribers felt "moderately" (5.0±1.9) concerned about APP (0–10), mostly due to chronic side effects (7.6±2.0), lack of evidence (7.1±2.2), non-adherence risk (6.7±2.3) and mortality risk (6.7±3.2), while increased cost (4.9±2.5) and higher total antipsychotic dose (4.2±2.9) ranked lowest. Comparing high with low APP prescribers (>10% vs. ≤10% of patients; mean: 36.1±19.8 vs. 3.4±3.4, $p<0.0001$), no differences emerged on 25/26 ratings regarding APP justification and 9/9 ratings regarding concerns. In a multivariate analyses, only attending status (OR=10.3, $p=0.0043$) and endorsing a specific APP preference (OR=21.4, $p=0.011$) predicted APP use >10% (r^2:0.35, $p<0.0001$), yet no uniformly preferred APP strategy emerged.
Conclusions: High APP prescribers had more clinical experience, less concerns about APP and more likely a preferred APP choice, although no overall preferred strategy emerged. Otherwise, high and low APP prescribers shared attitudes toward APP. Both had inherited most of their APP cases and were reluctant to convert patients to antipsychotic monotherapy.

Characteristics of AP Polypharmacy in Florida's Medicaid Insured Youth

Parameter	Age 6–12 y (n = 12,764)	Age 13–17 y (n = 10,419)
Users receiving monotherapy, no. (%)	11,925 (93)	9620 (92)
Users receiving polypharmacy, no. (%)*	839 (7)	799 (8)
No. of polypharmacy episodes	1426	1322
Duration of polypharmacy episodes, d		
Mean (SD)†	170.0 (139.0)	185.5 (175.9)
Median	120	121
Polypharmacy episodes per polypharmacy user		
Mean (SD)‡	1.7 (1.2)	1.7 (1.1)
Median	1	1
Range	1–11	1–9
Days from initiation of monotherapy to polypharmacy		
Mean (SD)§	505.8 (440.5)	384.9 (424.3)
Median	404	232

* χ^2 for age group by polypharmacy status = 10.49; $df = 1$; $P = 0.001$.
† $t = 2.57$; $df = 2746$; $P = 0.010$.
‡ $t = 0.80$; $df = 1636$; $P = 0.423$.
§ $t = 5.65$; $df = 1636$; $P < 0.001$.

Constantine RJ et al. Clin Ther. 2010 May;32(5):949-59.

Antipsychotic Combinations in Youth

Drug	Age 6–12 y		Age 13–17 y	
	Monotherapy (n = 6,064,176 days*)	Part of Combination (n = 279,562 days†)	Monotherapy (n = 3,674,322 days*)	Part of Combination (n = 271,124 days†)
Second-generation antipsychotics				
Risperidone	2,836,347 (47)	142,552 (51)	1,195,388 (33)	117,489 (43)
Quetiapine	1,339,344 (22)	155,324 (56)	1,117,371 (30)	147,397 (54)
Aripiprazole	972,602 (16)	145,257 (52)	602,623 (16)	111,293 (41)
Olanzapine	593,762 (10)	47,799 (17)	467,400 (13)	56,865 (21)
Ziprasidone	277,263 (5)	43,867 (16)	201,979 (5)	40,563 (15)
Clozapine	2671 (<1)	112 (<1)	14,393 (<1)	7776 (3)
Risperidone (depot)	255 (<1)	542 (<1)	7841 (<1)	4726 (2)
First-generation antipsychotics				
Thioridazine	11,289 (<1)	8661 (3)	17,515 (<1)	9555 (4)
Haloperidol	11,241 (<1)	9538 (3)	26,448 (1)	30,233 (11)
Pimozide	9795 (<1)	2113 (1)	3726 (<1)	1928 (1)
Chlorpromazine	6039 (<1)	7308 (3)	12,521 (<1)	18,215 (7)
Mesoridazine	1287 (<1)	480 (<1)	917 (<1)	916 (<1)
Trifluoperazine	1202 (<1)	659 (<1)	1675 (<1)	620 (<1)
Loxapine	402 (<1)	836 (<1)	309 (<1)	934 (<1)
Perphenazine	329 (<1)	1106 (<1)	1232 (<1)	2018 (1)
Fluphenazine	182 (<1)	512 (<1)	594 (<1)	932 (<1)
Thiothixene	91 (<1)	9 (<1)	1035 (<1)	960 (<1)
Molindone	66 (<1)	0	741 (<1)	937 (<1)
Haloperidol (depot)	9 (<1)	55 (<1)	445 (<1)	783 (<1)
Fluphenazine (depot)	0	0	169 (<1)	269 (<1)

Constantine RJ et al. Clin Ther. 2010 May;32(5):949-59.

Anticholinergic Use in Children and Adolescents After Initiation of Antipsychotic Therapy

Irene Seunghyun Hong and Jeffrey R Bishop

BACKGROUND: Second-generation antipsychotics (SGAs) are thought to have a lower likelihood of inducing extrapyramidal symptoms (EPS) than are first-generation antipsychotics (FGAs). Clinical observations suggest that younger patients may be more sensitive to SGA-associated EPS than are adults and require therapy with anticholinergic agents.

OBJECTIVE: To determine the proportion of patients 5–18 years of age who received anticholinergic therapy during the initial stages of antipsychotic treatment, as well as to compare anticholinergic utilization across patients receiving aripiprazole, risperidone, and quetiapine, SGAs previously identified as the most commonly prescribed at the academic institution studied.

METHODS: Patients 5–18 years of age who were initiating a course of an antipsychotic between January 1, 2005, and September 1, 2008, were identified in a retrospective review of prescription and medical records. Data on demographic characteristics, antipsychotic and anticholinergic utilization, indications, diagnoses, and concomitant medications were collected from the medical record. Only the first therapeutic course of an antipsychotic identified was analyzed. Anticholinergic utilization at antipsychotic initiation and after 30 days was assessed.

RESULTS: A total of 235 antipsychotic treatment courses were identified. Of these, 152 patients met our inclusion criteria. Anticholinergic utilization at any time during the first 30 days of treatment was identified in 32 patients (21%), while EPS was documented for 12 patients (8%). FGA or polypharmacy (simultaneous use of ≥2 scheduled antipsychotic) use versus SGA use (OR 18.98; 95% CI 4.74 to 75.95) was the primary characteristic significantly associated with anticholinergic utilization within 30 days after initiation. Of the most commonly used SGAs, risperidone was the drug with which anticholinergics were most frequently prescribed (p = 0.03).

CONCLUSIONS: Anticholinergic prescribing exceeded the incidence of EPS, as documented in the medical record (21% vs 8%), and differed across individual medications and antipsychotic class. Utilization of FGAs or polypharmacy was a key predictor of anticholinergic use.

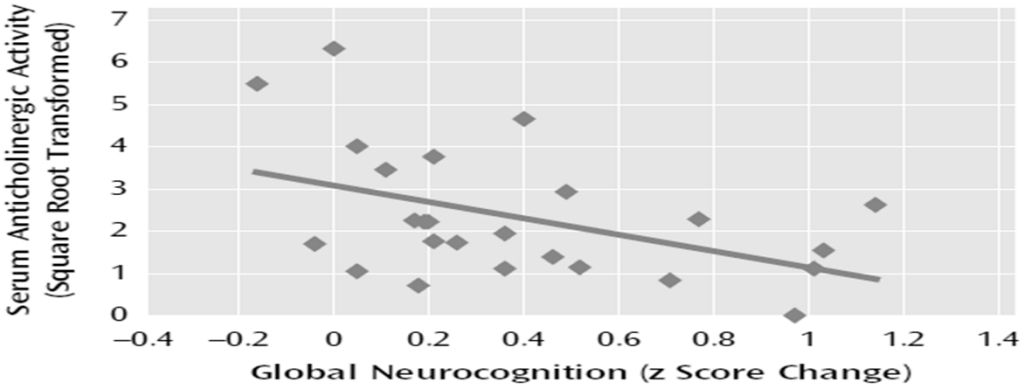
KEY WORDS: adolescent, anticholinergic, antipsychotic, extrapyramidal symptoms, pediatric.

Ann Pharmacother 2010;44:1171-80.

Published Online, 29 Jun 2010, *theannals.com*, DOI 10.1345/aph.1M643

Anticholinergic Load Reduces Learning

FIGURE 1. Association of Serum Anticholinergic Activity Level and Response to Computerized Auditory Training (Change in Global Cognition Score) in 25 Adult Patients With Chronic Schizophrenia[a]



[a] The bivariate correlation was −0.46 ($p<0.02$), while regression analysis revealed that serum anticholinergic activity level uniquely accounted for 20% of the variance in change in global cognition, independent of the effects of IQ, age, and symptom severity ($R^2=0.20$).

Vinogradov S. et al. Am J Psychiatry. 2009 Sep;166(9):1055-62.

Cross-Class Polypharmacy in Youth

• Analysis of the 1996-2007 National Ambulatory Medical Care Surveys data examining patterns in multiclass psychotropic treatment within a nationally representative pediatric outpatient sample consisting of 3,466 visits in which a psychotropic medication was prescribed.
• Across the 12 yr period, multiclass psychotropic treatment rose from 14.3% of child psychotropic visits (1996-1999) to 20.2% (2004-2007) (adjusted odds ratio [AOR] = 1.89, CI: 1.22-2.94, p < .01).
• Among medical visits in which a current mental disorder was diagnosed, the rate of multiclass psychotropic treatment increased from 22.2% (1996-1999) to 32.2% (2004-2007) (AOR = 2.23, 95% CI: 1.42-3.52, p < .001).
• There were significant increases in multiclass psychotropic visits in which ADHD medications, antidepressants, or antipsychotics were prescribed, and a decrease in those visits in which mood stabilizers were prescribed.
•There were specific increases in co-prescription of ADHD drugs and antipsychotic medications (AOR = 6.22, 95% CI = 2.82-13.70, p < .001) and co-prescription of antidepressant and antipsychotic medications (AOR = 5.77, 95% CI = 2.88-11.60, p < .001).

Comer JS et al. J Am Acad Child Adolesc Psychiatry. 2010 Oct;49(10):1001-10.

Evidence Base for Antipsychotic Polypharmacy in Adults

Meta-Analysis of RCTs of Antipsychotic Monotherapy vs. Combinations: N=19, n=1,216)

Timing: Costart at initiation: N=13, n=1009; Augmentation after non-response: N=6, n=207

Duration: 11.3±23.7; median: 8, range: 4-52 wks

Dosing: Comparative dose: N=13, n=789; Reduced dose: N=6, n=427

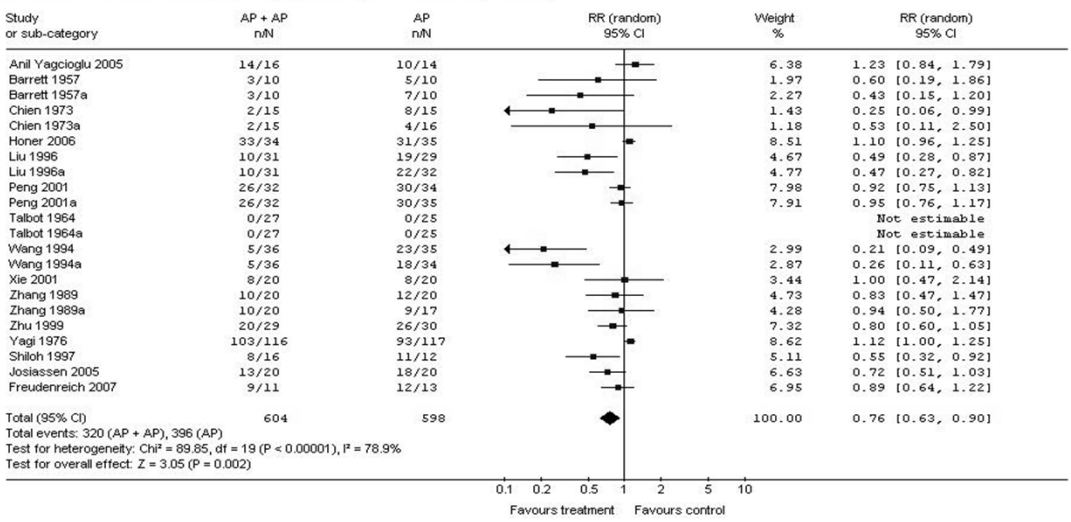
CPZ equivalents Co-Rx (N=8) vs. mono-Rx (N=12): 1141.6±464.4 mg/d vs. 723.3±327.0 mg/d, p=0.015)

CPZ equivalent dose ratio mono- vs. Co-Rx arms: 0.68±0.21 - but similar in studies favoring (N=7) vs. not favoring Co-Rx (N=5): 0.72±0.16 vs. 0.61±0.27, p=0.80)

Correll CU et al. Schizophr Bull. 2009 Mar;35(2):443-57.

Meta-Analysis of 19 RCTs of Antipsychotic Combinations: Inefficacy As Defined By Study

Review: Antipsychotic combinations for schizophrenia (Final_Reduced_Clean 1)
Comparison: 01 Comparison 1: 2 AP vs 1 AP (incl different dose and different AP)
Outcome: 04 Global state: 1. No clinically significant response - as defined by each study



N=22, n=1202, RR: 0.76, 95% CI: 0.63-0.90, p=0.002, NNT: 7, CI: 4-17, p=0.0008

Correll CU et al. Schizophr Bull. 2009 Mar;35(2):443-57.

Meta-Analysis of 19 RCTs of Antipsychotic Combinations: Efficacy Moderators

Sensitivity analyses:

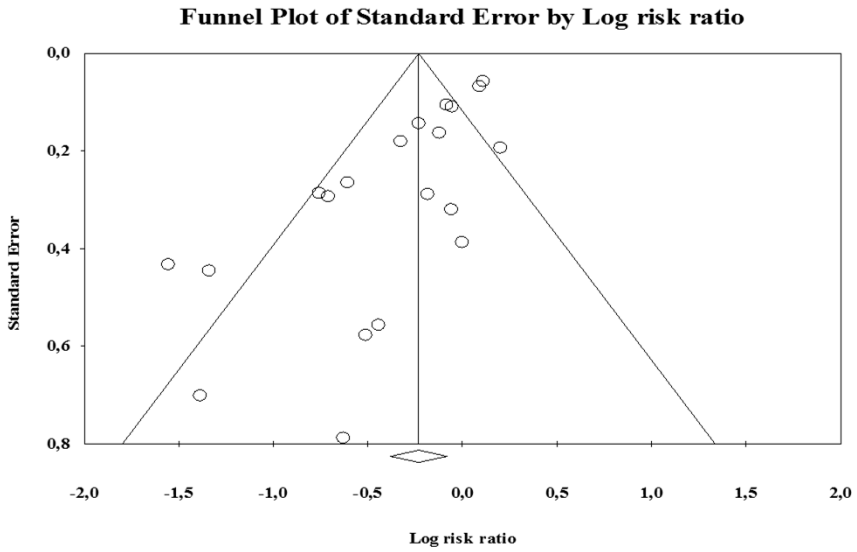
1. Study duration >/=10 weeks (p<0.0001)
2. Concurrent polypharmacy initiation (p=0.002)
3. Trials conducted in China (p=0.006)
4. Combinations including clozapine (p=0.008)
5. SGA + FGAs combinations (vs. FGA: p=0.04; vs SGA: p=0.009)

Meta-regression analyses:

1. Similar doses in mono- and polytherapy arm (p=0.006)
2. SGA + FGA combinations (p=0.027)
3. Concurrent polypharmacy initiation (p=0.05)

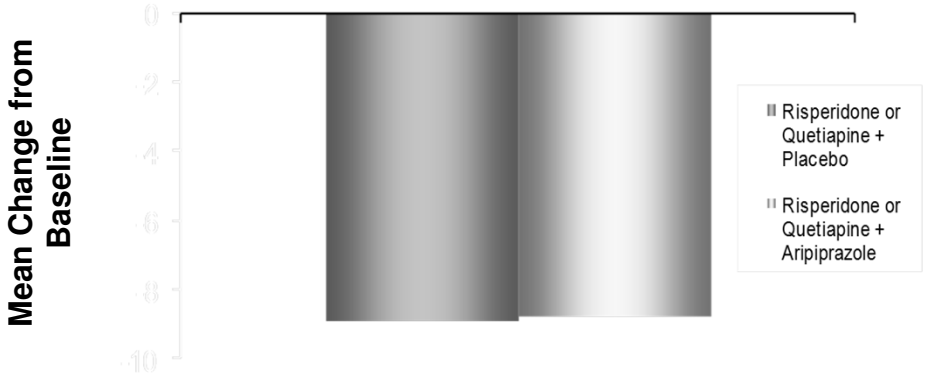
Correll CU et al. Schizophr Bull. 2009 Mar;35(2):443-57.

Meta-Analysis of 19 RCTs of Antipsychotic Combinations: Suggestion of Publication Bias



Correll CU et al. Schizophr Bull. 2009 Mar;35(2):443-57.

RIS or QUE + ARI vs PBO: Mean Change from Baseline to Endpoint in the PANSS total Score (Week 16, LOCF)

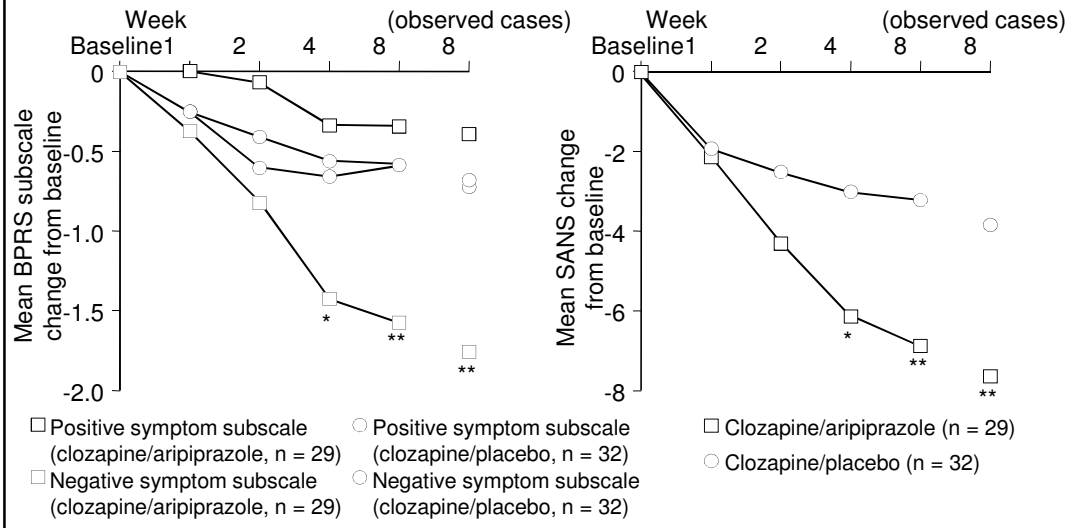


Mean PANSS Score at Baseline: Risperidone or Quetiapine + Placebo (n=155): 75.9

Risperidone or Quetiapine + Aripiprazole (n=168): 74.3

Kane JM et al. J Clin Psychiatry. 2009 Oct;70(10):1348-57.

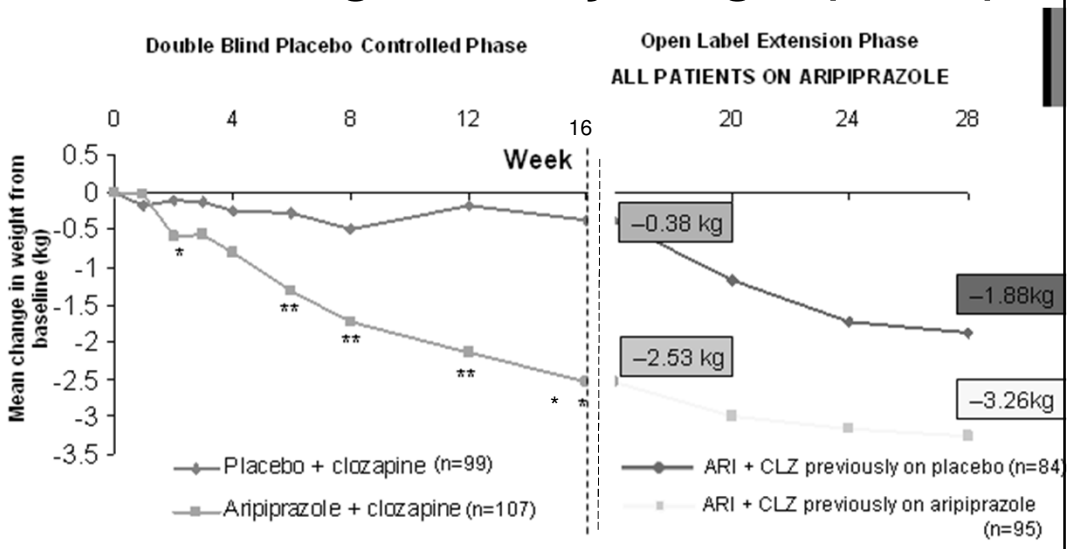
Aripiprazole (5-30 mg/d) Augmentation of Clozapine: Negative Symptom Change



*p<0.05 vs. placebo; **p<0.01 vs. placebo;
Greater improvement with ARI vs PBO in CGI-SI score (p=0.035) and YBOCS (p=0.013)
Greater reduction with ARI vs. PBO in triglycerides (-31.1 mg/dL vs 24.4 mg/dL, p=0.01) and non-HDL cholesterol (-13.5 mg/dLvs-3.7 mg/dL, p=0.05), despite similar change in weight (-1.2 kg vs -0.6 kg) and BMI (-0.4 vs -0.2)

Chang JS et al. J Clin Psych 2008; 69(5):720-31

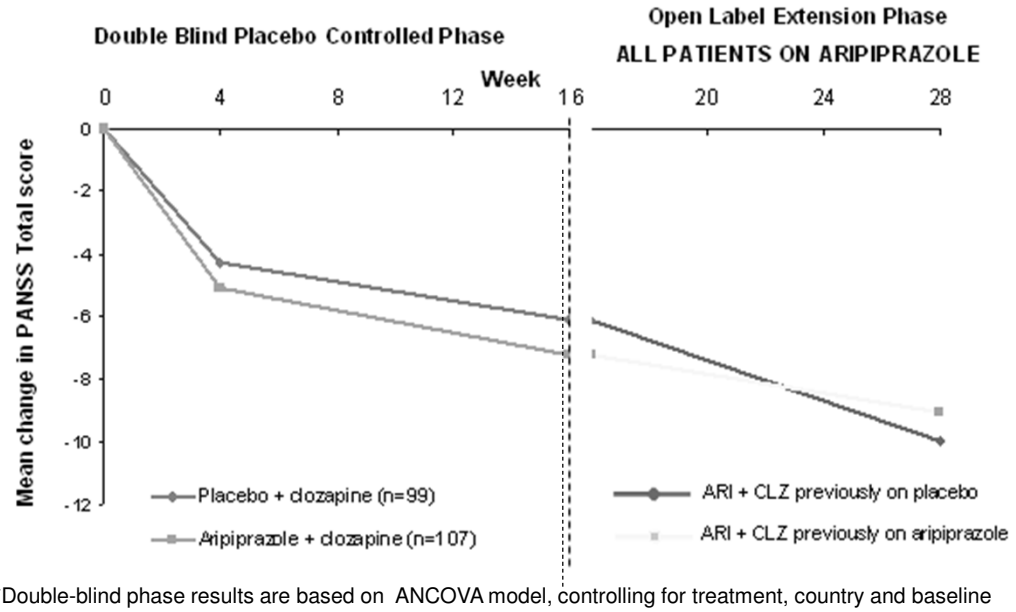
Mean Change in Body Weight (LOCF)



***p<0.05 vs. placebo; **p<0.001 vs. placebo;**
Baseline weight: PBO+ clozapine, 89.82 kg; aripiprazole + clozapine, 95.02 kg (p=0.031)
Weight loss >/= 7%: clozapine + PBO = 3% vs aripiprazole + clozapine = 15% (p=0.003)
Greater reduction with clozapine + ARI in total cholesterol (p=.002) and LDL-C (p=.003)

Fleischhhacker WW et al. Int J Neuropsychopharmacol. 2010;13:1115-1125

Change* in PANSS Total Score (LOCF)

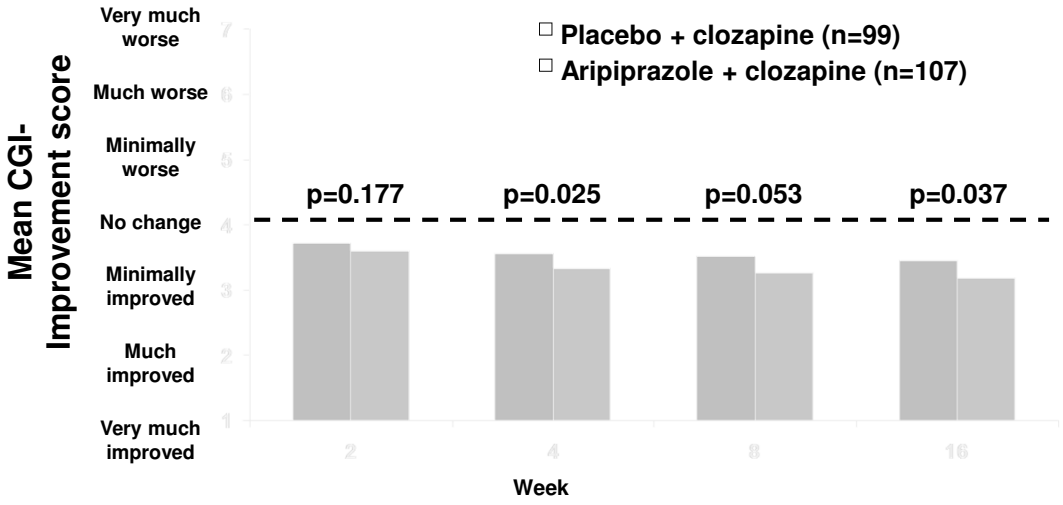


*Double-blind phase results are based on ANCOVA model, controlling for treatment, country and baseline PANSS score - - - Completion: Ari + CLO= 89.8%; PBO + Clo: 93.9%

Baseline mean PANSS Total scores: aripiprazole + clozapine, 72.6; placebo + clozapine, 71.2

Fleischhhacker WW et al. Int J Neuropsychopharmacol. 2010;13:1115-1125

Mean CGI-I Score (Double Blind Phase - Week 16*, LOCF)



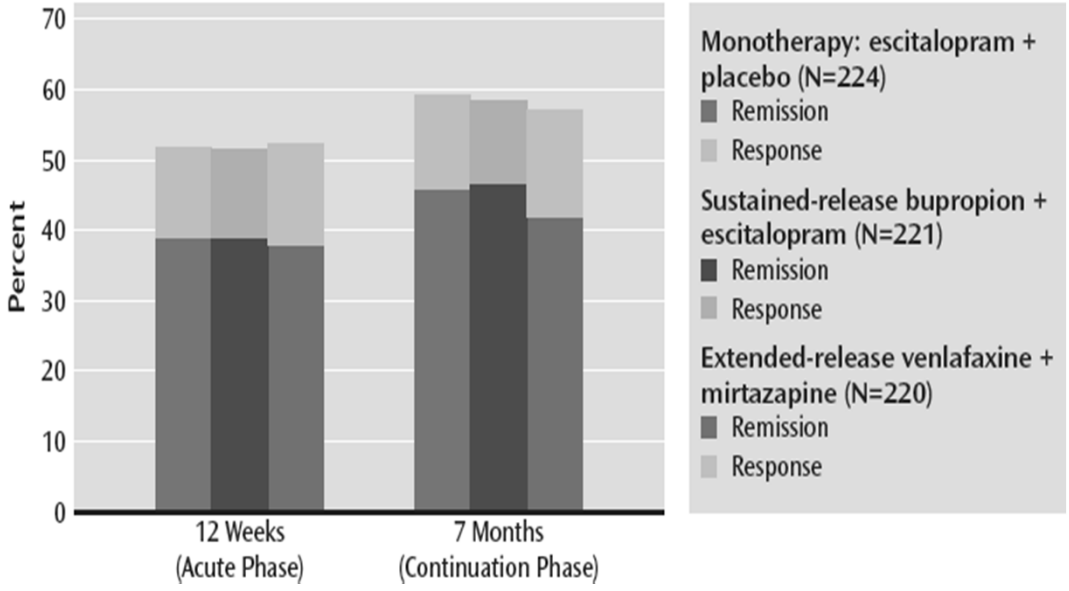
* These results are based on: ANCOVA model, controlling for treatment, country and baseline CGI-S Score

Fleischhhacker WW et al. Int J Neuropsychopharmacol. 2010;13:1115-1125

AP Polypharmacy: Adverse Effects

Side Effect	Increased: N Studies	Decreased: N Studies
EPS/Anticholinergic use	N= 19 (neutral: N=1)	N=1 (low HAL + low RIS)
Akathisia	N=1 (neutral: N=1)	N=0
Hyperprolactinemia	N=4	N=5 (AP+ARI), N=1 (LD HAL/RIS)
Sexual Dysfunction	N=1	N=2 (AP+ARI)
Weight gain	N=2 (neutral: N=4)	N=4 (CLO/OLA+ARI), N=2 (LD CLO+ZIP/QUE)
Dyslipidemia	N=2 (neutral: N=2)	N=5 (CLO/OLA+ARI)
Glucose elevation	N=2 (neutral: N=2)	N=1 (LD CLO+QUE)
Diabetes	N=3	N=0
Metabolic syndrome	N=1 (not independent: N=3)	N=0

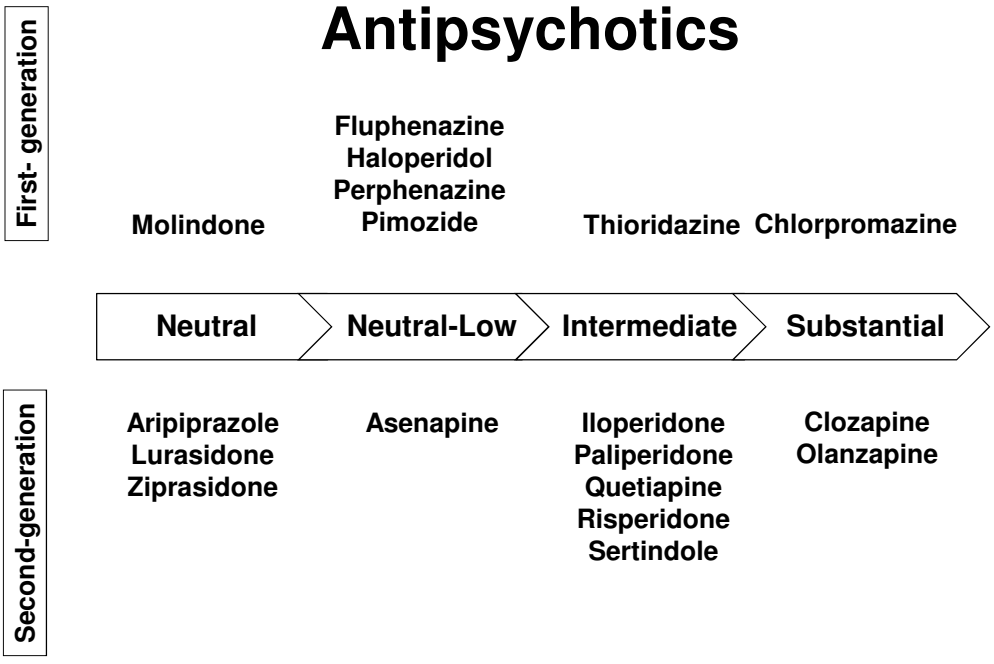
Combining Medications to Enhance Depression Outcomes (CO-MED): Acute and Long-term Outcomes of a Single-blind Randomized Study



Rush J et al. Am J Psychiatry 2011 Jul;168(7):689-701.

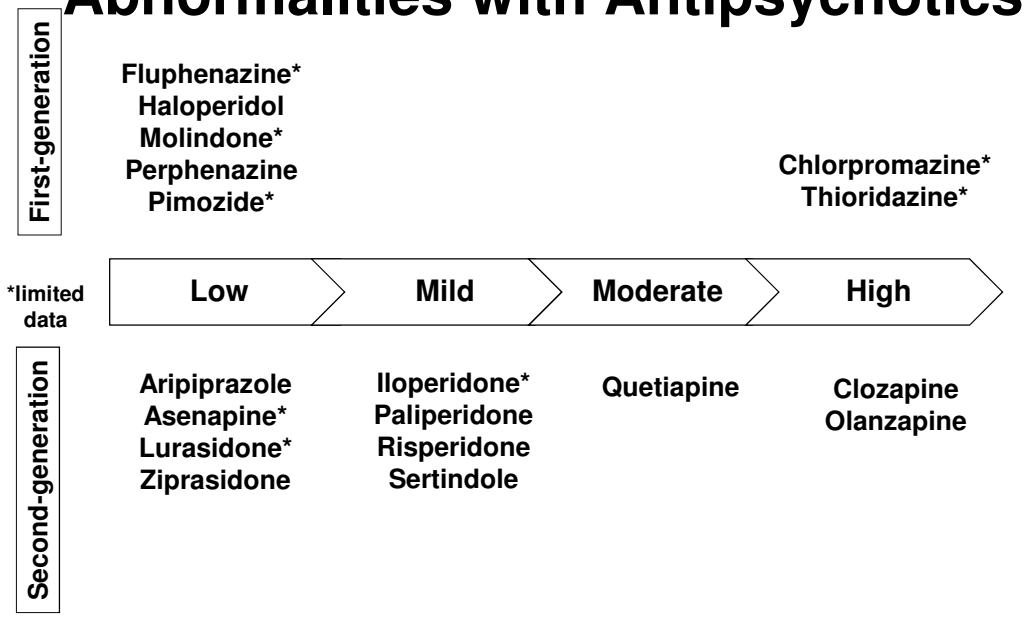
Cardiometabolic Risk Monitoring and Management

Risk of Weight Gain with Antipsychotics



De Hert M, Detraux J, van Winkel R, Correll CU. Nat Rev Endocrinol. 2011;8(2):114-26.

Risk of Lipid and/or Glucose Abnormalities with Antipsychotics



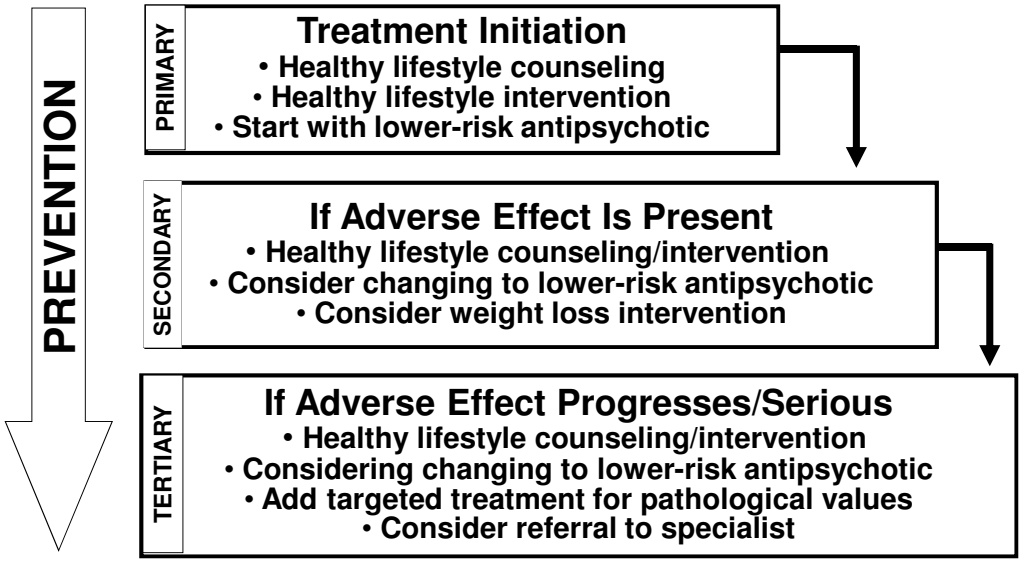
De Hert M, Detraux J, van Winkel R, Correll CU. Nat Rev Endocrinol. 2011;8(2):114-26.

Psychotropic Side Effect Monitoring in Youths

Assessments	Frequency
Personal and family history	Baseline and Annually
Lifestyle monitoring	Every visit
Height, weight, BMI percentile / z-score	Every visit
Somnolence/sedation	Every visit
Sexual symptoms/signs	Baseline, during titration and q 3 mo
Blood pressure, pulse	Baseline, 3-months and 6-monthly
Fasting glucose, lipids (if on APs)	Baseline, at 3 mo and (6-)12monthly
Liver function tests (if on APs)	Baseline, at 3 mo and (6-)12 monthly
EPS, akathisia	Baseline, titration, 3 mo and annually

Adapted from: Correll CU. *J Am Acad Child Adolesc Psychiatry*. 2008;47(1):9-20.

Medical Risk Management Strategies in Antipsychotic-Treated Patients



Correll CU. CNS Spectr. Vol 12. No 10 (Suppl 17), 2007: 12-20,35.

Conclusions 1

- Guidelines provide recommendations for a standardized treatment approach that is based on the evidence that is derived from mean scores in randomized controlled trials
- However, individualization of care is paramount to achieve best outcomes for specific patients
- Evidence in youth lags far behing that in adults
- Criteria for the best possible treatment approach include a balance between the highest possible levels of efficacy, tolerability, maintenance of effects, acceptance/adherence, subjective wellbeing and functionality
- Best clinical practices consist of combining evidence based and individualized approaches, using measurement and documentation as major quality tools

Conclusions 2

- Antipsychotic polypharmacy is common in adults the treatment of schizophrenia, even after the introduction of novel antipsychotics
- In youth, there is limited information, but there exists a subgroup of patients receiving AP Poly
- Controlled efficacy and safety data are slim, lacking or inadequate, and absent in youth
- Antipsychotic polypharmacy may be useful in certain scenarios, but, generally, monotherapy with adequate adherence, doses and duration should be attempted

Conclusions 3

- Given proven effectiveness of CLO for severe psychotic & mood d/o's, risks & benefits of co-treatments have to be weighed against CLO
- The same applies to ECT as a treatment option prior to antipsychotic polypharmacy
- Efficacy and adverse effect monitoring and management should be standardized
- Novel non-antipsychotic augmentation strategies and compounds require development and further study

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