CHILD & ADOLESCENT PSYCHIATRY ALERTS

Cannabis Use and Hypomania.....3
Group Metacognitive Therapy for Anxiety.....4
Lurasidone for Bipolar Depression.....1
Patient-Centered Outcomes in ADHD.....5
Reference Guide.....6
Suicide Risk in Sexual Minority Adolescents.....2

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Lurasidone in Bipolar Depression

In a manufacturer-sponsored, placebo-controlled trial in young patients with bipolar depression, treatment with lurasidone produced significant and clinically meaningful improvement in depression. Effects on weight and metabolic parameters were minimal.

Methods: Participants in this international study were young people, aged 10–17 years, with bipolar I disorder who were currently experiencing a major depressive episode of 1–12 months' duration. Participants were required to have a baseline score of ≥45 on the Children's Depression Rating Scale-Revised (CDRS-R) and ≤15 on the Young Mania Rating Scale (YMRS). Patients with rapid cycling (i.e., ≥4 but ≤8 mood episodes in the prior 12 months) or comorbid ADHD and receiving stable medication were not excluded from the study. Following a ≤3-week screening period, which included a taper of previous medications, patients were randomly assigned to double-blind treatment with lurasidone, flexibly dosed at 20–80 mg/day, or placebo. Concomitant stable stimulants for ADHD were permitted. The primary efficacy outcome was change from baseline to week 6 in CDRS-R total score. The key secondary outcome was change from baseline in the Clinical Global Impression–Bipolar Severity (CGI-BP-S) scale. Response was defined as a ≥50% reduction in the CDRS-R (after a reduction of 17 points to adjust for the scale's range), and remission as a composite of a CDRS-R score ≤28, a YMRS score ≤8, and a CGI-BP-S depression item score ≤3.

Results: A total of 343 patients (mean age, 14 years; 51% boys) were included in the primary efficacy analysis, including 39 who were taking stimulant medication for ADHD. The mean lurasidone dosage was 32.5 mg/day, but >50% of patients received the lowest dosage. More than 90% of patients completed the study.

Lurasidone was associated with a larger reduction in the CDRS-R total score than placebo (21 vs 15 points; $p<0.0001$; effect size,* 0.45). Changes from baseline in the CGI-BP-S averaged 1.49 and 1.05 points, respectively ($p<0.0001$; effect size, 0.44). Lurasidone appeared to be significantly more effective in reducing the CDRS-R in adolescents (aged 15–17 years)

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than in children (aged 10–14), largely due to a higher placebo response rate in the younger patients. More patients met response criteria with lurasidone than with placebo (60% vs 37%; p<0.0001; number needed to treat,* 5). Rates of remission (26% vs 19%; number needed to treat, 14) did not differ statistically between the groups. Lurasidone was also superior to placebo for other secondary measures, including anxiety, global functioning, and quality of life.

The most frequent adverse effects of lurasidone were nausea and somnolence. Rates of suicidal ideation were low and similar in the 2 groups. Compared with placebo, lurasidone was not associated with higher rates of emergent mania or hypomania (1.7% vs 2.3%), akathisia (2.9% vs 3.5%), or other extrapyramidal symptoms (2.3% vs 1.7%). Neurocognitive tests showed no deterioration in patients taking lurasidone. Changes in body weight and body mass index were similar in the 2 groups.

Discussion: There are few pharmacotherapy options for treating bipolar depression in children and adolescents. Recent clinical trials found quetiapine ineffective, and while fluoxetine–olanzapine is FDA approved for this indication, it is associated with high rates of intolerable adverse effects and clinically significant weight gain. These results, although they require replication, suggest that lurasidone may be a safe and effective option for this patient population.

Study Rating*—17 (100%): This study met all criteria for a randomized controlled trial.

DelBello M, Goldman R, Philips D, Deng L, et al: Efficacy and safety of lurasidone in children and adolescents with bipolar I depression: a double-blind, placebo-controlled study. *Journal of the American Academy of Child and Adolescent Psychiatry* 2017;56 (December):1015–1025. From the University of Cincinnati College of Medicine, OH; and Sunovion Pharmaceuticals, Marlboro, MA, and Fort Lee, NJ. **Funded by Sunovion Pharmaceuticals. All 6 study authors disclosed financial relationships with commercial sources including Sunovion.**

Common Drug Trade Names*: fluoxetine–olanzapine—*Symbyax*; lurasidone—*Latuda*; quetiapine—*Seroquel

***See Reference Guide.**

Suicide Risk in Sexual Minority Adolescents

Lesbian, gay, bisexual, and questioning adolescents were up to 3 or more times more likely to report suicidal behaviors than their heterosexual peers, according to the 2015 National Youth Risk Behavior Survey.

Methods: The survey was based on a representative sample that includes adolescents from all U.S. states and both public and private high schools. Students responded anonymously on computer-scannable paper questionnaires completed at school. They were asked whether, in the previous year, they had seriously considered suicide, planned suicide, or attempted suicide. Relative risks in comparison to heterosexual adolescents were calculated overall and by sexual minority subgroup and gender. The risk estimates were adjusted to represent the U.S. general adolescent population.

Results: Of a total of >15,600 adolescents surveyed, 89% identified themselves as heterosexual, 2% identified as lesbian, 6% as bisexual, and 3% as questioning. Among sexual minority youth, risks of all 3 types of suicidal behavior were elevated. Compared with heterosexual youth, adjusted risk ratios* in the minority groups were 2.45 for seriously considering suicide, 2.59 for planning suicide, and 3.37 for suicide attempt. Except for suicide attempts in the questioning group, in both heterosexuals and sexual minorities, risks of each type of behavior were generally higher in female than male adolescents. By minority subgroup, risks of each type of behavior were elevated in lesbian, gay, bisexual, and questioning adolescents, relative to heterosexuals. Rates of a suicide attempt in the past year ranged from about 15–23% in subgroups of sexual minority males and 12–34% in subgroups of sexual minority females.

Discussion: Nationally representative studies of suicide risk in sexual minority adolescents are rare and not sufficiently recent or detailed. Despite its limitations, the present survey suggests a need for research on effective suicide prevention in sexual minorities, as well as vigilance on the part of clinicians.

Caputi T, Smith D, Ayers J: Suicide risk behaviors among sexual minority adolescents in the United States, 2015 (letter). *JAMA* 2017;318 (December 19):2349–2351. From the Wharton School, University of Pennsylvania, Philadelphia; and other institutions. **Funded by the Joseph Wharton Scholar program; and other sources. The authors declared no competing interests.**

***See Reference Guide.**

Adolescent Cannabis and Hypomania

Cannabis use during adolescence was found to be an independent risk factor for hypomania symptoms in young adults in a population-wide cohort study. Cannabis use was also suggested as a candidate mechanism linking childhood abuse with later hypomania.

Methods: The Avon Longitudinal Study of Parents and Children birth cohort consisted of >14,000 children born in 1991–1992 in the county of Avon in southwestern England. Children were assessed annually in the clinic with interviews and physical and psychological tests. Cannabis use was assessed by participant report at age 17 years. Hypomania symptoms were measured when participants were aged 22–23 years using a mailed questionnaire, the 32-item Hypomania Checklist Questionnaire. The questionnaire was developed as a screening test for bipolar II disorder but has been validated for subclinical symptom assessment. Hypomania required a symptom threshold of 14 out of 32 during any lifetime episode of feeling high or "hyper," with negative consequences and ≥2–3 days of symptoms. The statistical model included additional variables such as family risk factors and physical and sexual abuse up to the age of 7 years (reported by the mother), adolescent-reported use of alcohol and illicit drugs, and psychotic and depressive symptoms in late adolescence.

Results: Data on hypomania symptoms in young adulthood were available for 3370 participants. The final analysis was weighted to compensate for the high attrition rate. After adjustment for potential confounders, cannabis use was associated with significantly elevated risk of hypomania in young adulthood. (See table.) Frequent cannabis use predicted hypomanic symptoms as well as depression and psychosis. A path analysis* showed that cannabis use was an independent risk factor for hypomania and also mediated the associations of male gender and childhood abuse with hypomania.

Adjusted associations between cannabis use at age 17 years and hypomanic symptoms at ages 22–23 years†

Cannabis Use	Odds Ratio*
Any cannabis use vs no cannabis use	1.42
Frequent use (≥2–3 times/week) vs less than weekly	2.21

†Adjusted for psychotic symptoms, depression, other drug use, hazardous alcohol use, gender, family adversity, and early childhood physical or sexual abuse

Discussion: The few prospective studies linking cannabis use with mania have focused on adult samples and have not always controlled for psychotic symptoms. The present finding of an association between adolescent cannabis use and later hypomania after controlling for alcohol and drug use and psychotic symptoms, along with the dose-response relationship, suggest the association may be directly causal. The authors suggest several potential mechanisms for the association: Alterations of reward system sensitivity via increasing dopaminergic signaling could underlie the association; harmful use of cannabis is more frequent in men than in women, and its use in men may be more important in the pathway

to hypomania; childhood physical and sexual abuse are indirectly associated with hypomania via increased risk of cannabis use.

Marwaha S, Winsper C, Bebbington P, Smith D: Cannabis use and hypomania in young people: a prospective analysis. *Schizophrenia Bulletin* 2017; doi 10.1093/schbul/sbx158. From the University of Warwick, U.K.; and other institutions. Funded by the UK Medical Research Council; and other sources. One of 4 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.

***See Reference Guide.**

Group Metacognitive Therapy for GAD

In an uncontrolled trial, group metacognitive therapy was an effective, acceptable treatment for generalized anxiety disorder in children.[1] Treatment effects were comparable to those previously found with cognitive behavioral therapy (CBT), the established therapy for childhood anxiety disorders.

Methods: Metacognitive therapy for children (MCT-c) is a manualized program developed by the authors, adapted from MCT for GAD in adults. MCT aims to teach a state of detached mindfulness, in which the patient notices but does not pay attention to worry-inducing negative thoughts. Study participants were self-referred families with a child, aged 7–13 years, who had a primary diagnosis of GAD. The therapy was delivered in 8 weekly 2-hour group sessions with 5–6 children and 3–4 therapists. Parents participated in 2-hour workshops prior to treatment and again 4 weeks into treatment. Children practiced attention training, shifting attention between their thoughts and stimuli in the environment, and detached mindfulness using in-session experiments, field trips, and other activities. Outcomes were assessed at the end of treatment and after 6 months.

Results: Study participants were 22 girls and 22 boys with confirmed GAD. The majority of patients had comorbid disorders; more than half had ≥2 additional diagnoses, usually but not exclusively other anxiety disorders. Half of the families had previously received psychological counseling or therapy for their child's anxiety. None of the children were taking psychotropic medications.

Of the 44 participating families, 43 completed treatment and 4 took advantage of optional booster sessions. At post-treatment, 38 children (86%) no longer met criteria for GAD and 32 (73%) were free of all anxiety disorders. At follow-up, 33 (75%) were free of GAD and 29 (66%) were free of all anxiety disorders. At both endpoints, children showed significant improvement on standardized measures of anxiety, with large effect sizes.* (See table.) Participants showed significant improvement on a validated measure of positive beliefs about the usefulness of worry, negative beliefs about the uncontrollability and dangerousness of worry, need to control thoughts, and cognitive self-consciousness. Cognitive confidence, was unchanged.

Change from baseline in standardized measures of anxiety

Measure	Effect Size	
	Pretreatment to posttreatment	Pretreatment to 6-month follow-up
Revised Child Anxiety and Depression Scale (RCADS)–child	1.20	1.26
RCADS–mother	1.29	1.28
RCADS–father	0.98	0.90
Penn State Worry Questionnaire for Children	0.95	1.04

Discussion: CBT is a well-established treatment for GAD in children, with an average effect size of 0.74, according to a recent meta-analysis.[2] Controlled trials comparing MCT with CBT appear to be warranted.

[1]Esbjørn B, Normann N, Christiansen B, Reinholdt-Dunne M: The efficacy of group metacognitive therapy for children (MCT-c) with generalized anxiety disorder: an open trial. *Journal of Anxiety Disorders* 2018;53 (January):16–21. From the University of Copenhagen, Denmark. **Funded by the Tryg Foundation; and other sources. The authors did not include disclosure of potential conflicts of interest.**

[2]Ishikawa, S, et al: Cognitive behavioural therapy for anxiety disorders in children and adolescents: a meta-analysis. *Child and Adolescent Mental Health* 2007;12 (4):164–172.

***See Reference Guide.**

Measuring Patient-Centered Outcomes in ADHD

A systematic review of randomized trials indicates that in patients with ADHD functional impairment and health-related quality of life (HRQoL) generally improve with drug treatment. Effects appear to be larger in children and adolescents than in adults and with stimulants versus non-stimulant medications.

Background: It is now widely acknowledged that treatment of ADHD should aim to improve function and HRQoL, in addition to improving ADHD symptoms. Assessing these outcomes typically relies on completion of a questionnaire by the patient or by a proxy such as a parent or teacher. The 2 outcomes share similarities, but functional impairment is generally considered to be objective and ideally assessed by unbiased methods, while HRQoL is considered to be subjective and best rated by the patient. It is important to use measures that do not merely mirror changes in ADHD symptoms.

Methods: The systematic review included English-language papers, published in peer-reviewed journals, which reported placebo-controlled studies of ADHD medications with analyses of functional outcomes or HRQoL. Study designs could be parallel-group, crossover, treatment initiation, or treatment withdrawal. The reviewers did not formally assess risk of bias, but noted that because the outcomes of interest are usually secondary efficacy measures, they may be less likely to be reported than primary outcomes. Post-hoc analyses were excluded for this reason. A meta-analysis could not be conducted because of the diversity of study designs, populations, medications, and outcome measures. To reduce bias, the analysis reported effect sizes,* with a cutoff of 0.50 as a threshold for clinical relevance.

Results: The analysis was based on 34 studies, 18 in children and adolescents and 16 in adults. A total of 14 investigated stimulants, and 21 investigated non-stimulants. Almost all were short-term, with treatment lasting ≤20 weeks.

HRQoL was proxy-rated by parents in nearly all child and adolescent studies. The most frequently used instrument to measure HRQoL was the Child Health and Illness Profile-Child Edition: Parent Report Form. Children and adolescents with ADHD had substantially reduced HRQoL before treatment, with average scores 1.5–2.0 standard deviations below population norms in domains reflecting achievement and risk taking. Of 12 studies that reported HRQoL, 10 reported improvement in ≥1 domain or summary measure, with the largest improvements in domains related to achievement and risk taking. In the most responsive domains, effect sizes were larger for stimulants (range, 0.54–1.28) than for non-stimulants (range, 0.29–0.87).

Function was often measured using the Weiss Functional Impairment Rating Scale–Parent. Children and adolescents showed fairly consistent improvement in the Family and Learning and School domains. Effect sizes in responsive domains ranged from 0.86 to 1.25 for stimulants and from 0.32 to 0.58 for non-stimulants.

Severity of and improvement in ADHD symptoms were correlated moderately to strongly, but not perfectly, with improvements in function and HRQoL. Improvements were greatest in domains related to school or achievement, risk taking, and interpersonal relationships, the domains with the greatest deficits at baseline. Studies reported larger effect sizes for ADHD symptoms than for HRQoL and functional outcomes.

Discussion: Poor HRQoL and functional impairment relate to ADHD symptoms but are distinct, reflecting the impact of the disorder on patients' daily lives. The results of this analysis suggest that improving function and quality of life should be an important aim of ADHD treatment. They do not, however, address whether improvements in function and HRQoL are directly related to pharmacotherapy, improvements in symptoms, or both.

Study Rating*—16 (89%): This study met most criteria for a systematic review, but individual study quality was not assessed.

Coghill D, Banaschewski T, Soutullo C, Cottingham M, et al: Systematic review of quality of life and functional outcomes in randomized placebo-controlled studies of medications for attention-deficit/hyperactivity disorder. *European Child and Adolescent Psychiatry* 2017;26 (November):1283–1307. From the University of Melbourne, Australia; and other institutions. **Funded by Shire International GmbH. All 5 study authors disclosed financial relationships with commercial sources.**

***See Reference Guide.**

Reference Guide

Effect Size: The effect size represents the amount of change in outcome that can be attributed to treatment, where 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect. It is relatively independent of clinical significance, and large effect sizes do not ensure treatment efficacy.

Number Needed to Treat: Indicates how many patients need to be treated for 1 to benefit. The ideal NNT is 1, where everyone improves with treatment. The higher the NNT value, the less effective is the treatment.

Odds Ratio: A comparison of the probability of an event in 2 groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison group.

Path Analysis: A method employed to determine whether or not a multivariate set of nonexperimental data fits well with a particular (a priori) causal model.

Risk Ratio: The risk of an event (or of developing a disease) relative to exposure. Relative risk is a ratio of the probability of the event occurring in the exposed group versus the control (non-exposed) group.

Study Rating: A measure of how well a study conforms to quality standards. The study rating uses a checklist system based on the comprehensive Strength of Evidence Report from the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality (AHRQ). The rating checklists are posted at www.alertpubs.com.

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