Generic Concerta: Therapeutic Equivalence

Based on results of an analysis of adverse event reports and laboratory tests, the FDA has expressed concern about the therapeutic equivalence of 2 generic extended-release methylphenidate formulations. In some patients, the generic products manufactured by Mallinckrodt and Kudco may release active drug at a slower rate than brand-name Concerta. This can inhibit the desired therapeutic effects. Although there are no serious safety concerns and the agents remain FDA approved, they are no longer recommended as automatically substitutable for Concerta at the pharmacy level. The FDA has requested the manufacturers confirm the bioequivalence of their products using revised standards within 6 months or withdraw their products from the market.


Dialectical Behavior Therapy for Self-Harm

In a randomized trial, dialectical behavior therapy (DBT) was superior to active control therapies in reducing self-harming behavior in adolescents with borderline personality disorder traits.

**Background:** DBT is known to be effective in prevention of self-harm in adults. In order to examine efficacy in self-harming adolescents with elements of borderline personality disorder, the therapy was adapted by reducing the duration from 12 months to 3–5 months, by including parents in weekly skills training groups, and by adding a skills module specifically for teens with emotion dysregulation.

**Methods:** Study participants were 77 adolescents, aged 12–18 years, who were referred from pediatric psychiatric clinics. To be included, patients had to have a history of ≥2 episodes of deliberate self-harm, including a recent one, and to meet 2 DSM-IV criteria for borderline personality disorder, or 1 criterion plus 2 subthreshold criteria. Participants were randomly...
assigned to 19 weeks of either the adapted DBT program for adolescents (DBT-A) or enhanced usual care, which could be either no less than weekly psychodynamic therapy or as-needed cognitive behavioral therapy with medication. The primary study outcomes, assessed by blinded raters, were the number of patient-reported self-harm episodes, suicidal ideation (measured with the Suicidal Ideation Questionnaire), suicidal thoughts on a Likert scale, and level of depressive symptoms (measured with the Montgomery-Asberg Depression Rating Scale and the Short Mood and Feelings Questionnaire).

**Results:** The average numbers of self-injury episodes per week were similar for the 2 treatments at baseline and early in therapy. The number of episodes decreased with treatment in both groups. In weeks 10–15, patients who received DBT-A reported significantly fewer self-harm episodes: 1.2 per week, compared with 3.3 for the usual care group (p=0.021 for the between-group difference). Both groups had decreases in suicidal ideation, which were larger with DBT-A (p=0.01). Both measures of depressive symptoms also showed greater improvement with DBT-A than with the control treatments, as did borderline symptoms and a measurement of hopelessness. Effect sizes for all of these outcomes were large in the DBT-A group (ranging from 0.86 to 0.97) and low to medium in the usual-treatment group (0.16 to 0.41).

Mehlum L, Tormoen A, Ramberg M, Haga E, et al: Dialectical behavior therapy for adolescents with repeated suicidal and self-harming behavior: a randomized trial. *Journal of the American Academy of Child and Adolescent Psychiatry* 2014;53 (October):1082–1091. From the University of Oslo, Norway; and other institutions. Funded by the Norwegian Directorate of Health; and other sources. The authors declared no conflicts of interest.

### Psychosocial Treatments for Self-Injurious Thoughts and Behaviors

Several psychosocial treatments show promise in treating self-injurious thoughts and behaviors (SITBs) in young people, according to a systematic review.

**Methods:** The review included studies published through September 2013, as well as in-progress or recently completed studies available on clinicaltrials.gov. Randomized controlled trials, non-randomized trials, and pilot studies were all considered. To be included in the review, studies were required to examine interventions for at-risk patients aged <19 years, specifically designed to treat SITBs (rather than primary disorders with SITB as a feature), and that measured a specific SITB outcome. Outcomes included nonsuicidal self-injurious behavior as well as suicidal ideation and behavior.

**Results:** A total of 29 studies were identified with interventions that included cognitive behavioral therapy (CBT), dialectical behavior therapy, family-based treatments, interpersonal therapy, combined skills group therapy, and other intervention techniques. Of the studies, 18 were randomized trials, 5 were nonrandomized trials, and 6 were pilot studies. The treatments represented a variety of theoretical orientations, including cognitive behavioral, family, interpersonal, and psychodynamic.

None of the therapies was supported by ≥2 well-designed clinical trials from independent research settings showing superiority to medication or placebo or equivalence or superiority to another established treatment (the authors’ criteria for a well-established treatment). Five treatments met criteria for "probable" efficacy, which included valid methods and superiority to an active treatment, psychological placebo, or medication. Each was supported by a single controlled trial. The promising treatments were: a combination of family and individual CBT with parent training; 2 types of family-based therapy; individual interpersonal therapy; and individual and family psychodynamic therapy. Target outcomes in these studies ranged from deliberate self-harm to suicide attempts. A sixth therapy, ecological family-based therapy, met criteria for "possible" efficacy, in part because of design limitations of the single clinical trial. The remaining treatments were classified as "experimental" or of "questionable" efficacy.
Discussion: Because no single theoretical orientation appears to be superior to others in reducing SITBs, treatment efficacy is likely the result of elements shared by the therapies. Promising treatments shared a focus on relationships or interpersonal function; inclusion of the family or parents; individual skills training; an intensive focus (i.e., greater treatment length and number of weekly contacts); and targeting other maladaptive behaviors or risk factors, specifically substance use.

In the absence of established treatments for SITBs, clinicians may want to consult evidence-based clinical guidelines for suicidal youth, which include clinical assessment, crisis management, and hospitalization. Therapies aimed at reducing SITBs are resource-intensive and long-term, and it is unclear which components are effective. There is a need for development of brief interventions for high-risk crisis periods, when long-term interventions may be inadequate. Data suggest that safety planning in a single-session to limit access to lethal means may prevent suicide attempts.

Glenn C, Franklin J, Nock M: Evidence-based psychosocial treatments for self-injurious thoughts and behaviors in youth. Journal of Clinical Child and Adolescent Psychology 2014; doi 10.1080/15374416.2014.945211. From Harvard University, Boston, MA. Funded by the NIMH; and other sources. The authors did not include disclosure of potential conflicts of interest.

Second-Line Therapy for OCD: CBT vs. Sertraline

In a controlled trial, children and adolescents with obsessive-compulsive disorder who did not respond to first-line cognitive behavioral therapy did equally well whether they continued with CBT or were switched to sertraline (Zoloft).

Methods: This randomized trial was part of the Nordic Long-Term OCD Treatment Study (NordLOTS), an ongoing investigation of stepped care for OCD in patients aged 7–17 years. The study was conducted in 3 Scandinavian countries. To maximize generalizability, exclusion criteria for the study were kept to a minimum. The initial treatment step (step 1) consisted of 14 individual weekly sessions of exposure-based CBT. Participants who continued to have moderate-to-severe OCD symptoms, with a Children’s Yale-Brown Obsessive Compulsive Scale (CY-BOCS) score ≥16, were randomly assigned to 1 of the 2 manualized step 2 treatments. Sertraline therapy was provided with a target dosage of 100 mg/day, and a maximum of 200 mg/day for resistant symptoms. Clinicians were instructed to encourage patients to practice exposure tasks learned in step 1, but no new tasks were introduced. Patients who were assigned to continued CBT received 10 additional sessions over 16 weeks, with specific attention to barriers that might have interfered with step-1 treatment. The primary outcome measures were the CY-BOCS total score and response (CY-BOCS, ≤15) after 30 weeks.

Results: Of 66 non-responders to step 1, 12 refused randomization and 4 improved during the evaluation period, leaving 50 eligible for randomized step-2 treatment. A total of 28 were assigned to continued CBT, and 22 to sertraline. Seven patients in each group withdrew consent for treatment but were included in the intent-to-treat efficacy analysis.* About one-fourth of the patients had demonstrated substantial reductions (30–47%) in CY-BOCS scores with step-1 treatment but continued to meet the severity criterion for step 2.

At week 30, both treatment groups showed substantial improvement with no significant difference in outcome between the 2 treatments. Response rates were 50% with continued CBT and 45% with sertraline. Almost one-third of all participants had a CY-BOCS score of ≤10, indicating remission, at the final assessment. The effect sizes* for both treatments were comparable: 1.04 for continued CBT and 1.19 for sertraline. Both treatments had similar effects on the Child Obsessive-Compulsive Impact Scale (COIS), a parent- and child-rated
scale that measures the impact of OCD on home, social, and school environments. However, patient-rated improvement on the COIS was significantly greater for sertraline than CBT.

**Discussion:** CBT is the recommended first-line treatment for pediatric OCD, but studies suggest that 40% of patients fail to show an adequate response. This is the first known randomized trial of the efficacy of second-line treatments in pediatric OCD. In the NordLOTS study, second-line treatments continued to increase the response rate, from 73% in step 1 to a total combined response rate of 81%. This study did not investigate combined CBT and SSRI therapy as a step-2 option, but this approach in nonresponders to CBT monotherapy is not supported by empirical data.

Skarpheinsson G, Weidle B, Thomsen P, Dahl K, et al: Continued cognitive-behavior therapy versus sertraline for children and adolescents with obsessive-compulsive disorder that were non-responders to cognitive-behavior therapy: a randomized controlled trial. *European Child and Adolescent Psychiatry* 2014; doi 10.1007/s00787-014-0613-0. From the Center for Child and Adolescent Mental Health, Oslo, Norway; and other institutions. Funding was provided individually at each national site and was supplied by TrygFonden; The Danish Council for Strategic Research; and other sources. The authors declared no competing interests.

*See Reference Guide.

**ADHD, Stimulants, and Sexual Maturation**

Neither ADHD nor stimulant medications delayed sexual development in early puberty, according to the results of a cross-sectional study.

**Methods:** A secondary analysis was conducted in participants in the Multimodal Treatment Study of Children with ADHD. The analysis included 342 participants with ADHD and 159 age- and gender-matched local controls. At the time of evaluation, participants were aged 10–14 years (mean age, 12 years). Stimulant use was assessed for the preceding 36 months. Among those with ADHD, 56 had never used stimulants and 116 were inconsistent users. The remaining 135 participants had used stimulants consistently throughout the observation period. Sexual maturation was assessed by self-reported and clinician-reported Tanner stage and by auxology, a method that imputes maturation from physical growth data.

**Results:** Tanner ratings of the patients and clinicians showed high agreement. There were no differences between the group with ADHD and the comparison group in genital development or the onset of pubic hair growth. Medicated and unmedicated patients with ADHD did not differ in sexual maturation rating using either Tanner stages or the auxological approach. There was a trend toward a delayed adolescent growth spurt in children taking stimulants.

Greenfield B, Hechtman L, Stehli A, Wigal T: Sexual maturation among youth with ADHD and the impact of stimulant medication. *European Child and Adolescent Psychiatry* 2014;23:835–839. From Montreal Children's Hospital and McGill University, Canada; and other institutions. Funded by the NIMH. The authors declared no competing interests.

**Sequential Therapy for Relapse Prevention in Depression**

In a randomized trial, sequential treatment with targeted cognitive behavioral therapy (CBT) reduced the rate of relapse in young patients who had experienced response to acute pharmacotherapy for depression.

**Methods:** Study subjects (n=200) were children, aged 8–11 years, and adolescents, aged 12–17 years, with major depressive disorder of at least moderate severity. All participants received open-label fluoxetine (*Prozac*) for 6 weeks plus medication management visits with supportive care but no specific psychotherapy. Those who experienced response (≥50% reduction in the Children's Depression Rating Scale–Revised (CDRS-R; n=144) were then randomly assigned to continue on medication alone or to receive, in addition, relapse-prevention CBT for 6 weeks. The therapy was delivered in 2 sessions (1.5 hours each) with the patient and parents, followed
by 6–9 individual sessions (1 hour each). CBT was flexible and focused on improving residual symptoms, increasing periods of well-being, relapse prevention, and addressing specific risk factors for relapse. Medication-management visits were continued throughout the 6 months in both treatment groups. The 2 primary study outcomes, evaluated by blinded raters, were time to remission (CDRS-R total score, ≤28) and rate of relapse (CDRS-R, ≥40 for ≥2 weeks, or significant clinical deterioration).

**Results:** The average time to remission was 11 weeks from the start of fluoxetine therapy for the CBT group and nearly 14 weeks for the group that received medication alone (p=ns). Remission rates did not differ between the 2 groups at any time point. At the end of follow-up, remission rates were 90% in the CBT group and 84% in the medication group.

The CBT group had a markedly reduced risk of relapse (hazard ratio,* 0.313; p=0.01). Relapse rates in this group were lower than the medication-only group throughout the study. By the end of treatment, 9% of the CBT group and 27% of the medication-only group had relapsed. The mean time to relapse was the same in the 2 groups, at about 28 weeks. The CBT group also required significantly lower maximum fluoxetine doses than the medication management group.

**Discussion:** This is one of very few studies of continuation therapies in pediatric depression. While the CBT was designed to prevent relapse, the investigators suspected it might also shorten time to remission. At 2 weeks, the difference proved not to be statistically significant, but it may still be clinically meaningful. Sequencing may be an efficient way to treat, because it reduces the traditional number of CBT sessions (12–16) required for a positive outcome.

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

Kennard B, Emslie G, Mayes T, Nakonezny P, et al: Sequential treatment with fluoxetine and relapse-prevention CBT to improve outcomes in pediatric depression. *American Journal of Psychiatry* 2014;171 (October):1083–1090. From the University of Texas Southwest Medical Center, Dallas; and Children’s Medical Center of Dallas. **Funded by the NIMH.**

One study author declared financial relationships with commercial sources. The remaining 6 authors declared no conflicts of interest.

*See Reference Guide.

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**Magnetic Seizure Therapy for Bipolar Depression**

In what appears to be the first reported use in an adolescent, magnetic seizure therapy (MST) produced rapid remission of symptoms an adolescent male patient with treatment-resistant bipolar depression.¹

The 18-year-old male had undergone multiple unsuccessful trials of antidepressants, antipsychotics, and mood stabilizers over 12 months before being referred for repetitive transcranial magnetic stimulation (rTMS). He experienced partial response with rTMS but continued to have a Hamilton Rating Scale for Depression (HAM-D) score of 9. Improvement was transient, his HAM-D score worsened to 21, and he was referred for a trial of MST. All medications were stopped with the exception of thyroxine for mild hypothyroidism. The MST protocol comprised 18 acute sessions administered over 6 weeks, followed by an additional 9 continuation sessions over 6 months. After the patient’s 12th MST session, his HAM-D score was reduced to 10. By the end of acute treatment, the score was further reduced to 8 and he met criteria for remission (HAM-D ≤10, plus a ≥60% reduction in scores on 2 consecutive assessments). Continuation treatment was completed to prevent relapse and during this phase his HAM-D score ranged from 3 to 6. Cognitive function was within normal limits during treatment. The patient had severe nausea after the first session, but this was controlled with antiemetics at subsequent sessions. He experienced prolonged...
seizures during 11 of the 27 MST sessions that required pharmacological termination. Remission was maintained during 11 months of follow-up.

MST uses methods similar to rTMS but with higher frequencies of stimulation that unlike rTMS are designed to induce seizures. The treatment has been shown to have antidepressant efficacy in adults with no apparent cognitive side effects.2

1Noda Y, Daskalakis Z, Downar J, Croarkin P, et al: Magnetic seizure therapy in an adolescent with refractory bipolar depression: a case report. Neuropsychiatric Disease and Treatment 2014;10:2049–2055. From the University of Toronto, Canada; and other institutions. Five of 6 study authors declared financial relationships with commercial sources, including 3 with Brainsway a manufacturer of rTMS devices; the remaining author declared no conflicts of interest.


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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.

Hazard Ratio: A measure of the risk of an event relative to exposure, or the probability of an event occurring in an exposed group versus a non-exposed group. A hazard ratio of 0.5 indicates that 1 group has half the risk of the other group.

Intent-to-Treat (ITT): An analysis based on initial treatment intent, not on the treatment actually administered or completed. In an ITT analysis, everyone who begins treatment is regardless of treatment completion. ITT analyses are done to avoid the effects of crossover, drop-out, and other factors that could alter the results or inflate the magnitude of effects.

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 have been posted at www.alertpubs.com.