Chewable Methylphenidate ER

The FDA has granted approval for the first chewable formulation of extended-release methylphenidate (QuilliChew ER). In a clinical trial of children aged 6–12 years with ADHD, QuilliChew improved both attention and behavior beginning 45 minutes after ingestion and lasting through an 8-hour laboratory classroom challenge. The new formulation, for use in patients aged ≥6 years, will be available in 20-, 30-, and 40-mg tablets that can be taken with or without food and is expected to be in pharmacies in the first quarter of 2016. The recommended starting dosage is 20 mg/day and dosages >60 mg/day are not recommended. As with other stimulants, patients should be evaluated for cardiac disease before starting treatment with QuilliChew and use is contraindicated with concurrent or recent MAOI use. QuilliChew contains phenylalanine, which can be harmful to patients with phenylketonuria. Adverse effects appear to be similar to other methylphenidate formulations.


Technology-Assisted CBT for Adolescent Depression

A technology-enhanced program was useful in training therapists in cognitive behavioral therapy for adolescent depression and in enhancing the therapeutic alliance.

Background: The present study was conducted by the developers of the technology-enhanced CBT protocol (available at http://telepsychology.net/default.aspx) and funded by the NIMH as part of the institute’s initiative to develop technological enhancements of evidence-based treatments. The online training module was developed to address “a critical shortage of CBT-trained therapists.”

Methods: The study recruited 18 clinicians without prior accreditation or formal training in CBT. Each clinician was randomly assigned to either CBT or their usual treatment methods, and each provided treatment for 4 adolescents recruited from his or her practice for 12 weeks.
using CBT or usual methods. The enhanced-CBT protocol had 3 components: therapist training, in-session use of tablet computers to convey CBT concepts and skills, and between-session text messaging for homework reminders and self-monitoring. The training consisted of an online tutorial based on the NIMH manual for CBT in adolescent depression and took an average of about 5.5 hours to complete. Trained therapists were then given a tablet with access to materials for use with patients. Between-session text reminders were sent with a timing and frequency set collaboratively by the patient and clinician, typically twice a day. The primary clinical outcome measure was the patient-reported Quick Inventory of Depressive Symptomatology—Adolescent (QIDS-A). Other outcome measures were a pre- and post-test of CBT principles for the clinician and standardized measures of user satisfaction and the therapeutic alliance for both clinician and patient.

**Results:** After participating in the online training tutorial, clinicians demonstrated a significant (p<0.001) increase in knowledge of CBT concepts, and virtually all of the program’s 23 specified learning objectives were met. Clinicians gave the program high ratings for clarity, usefulness of content, and user-friendliness and said that they were likely to recommend it to others. Clinicians also gave good-to-excellent ratings to various aspects of the in-session teaching materials. Among adolescents, ≥85% said that the in-session materials and text messaging were helpful in learning new material and enhancing the effectiveness of homework.

Mean scores on the QIDS-A showed improvement in depressive symptoms, which were numerically but not statistically larger in adolescents who received CBT, with a small effect size* (0.08) relative to treatment as usual. The therapeutic alliance was rated significantly higher with CBT than treatment as usual among both patients (p=0.03) and clinicians (p=0.001).

**Discussion:** This study demonstrates the feasibility of technology-assisted CBT as an enhancement of existing treatment, rather than as a lower-intensity replacement designed to save therapists’ time, as with recent technology-based stepped-care models. The small-but-real effect size should be viewed as encouraging, possibly suggesting a need for additional in-person CBT training. The improvement in therapeutic bond with the technology could help keep adolescents in treatment.

Kobak K, Mundt J, Kennard B: Integrating technology into cognitive behavioral therapy for adolescent depression: a pilot study. *Annals of General Psychiatry* 2015; doi 10.1186/s12991-015-0077-8. From the Center for Telepsychology, Madison, WI; and the University of Texas Southwest Medical Center, Dallas. Funded by the NIMH; and other sources. All study authors declared relevant financial relationships.

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**Parent Interventions for Disruptive Behavior**

Psychosocial interventions for childhood disruptive behavior disorders are most effective when they include a parent component, according to a systematic review and meta-analysis of comparative studies.

**Background:** The use of outpatient psychotherapy for childhood behavior disorders is declining, and medication-only approaches are increasing. While this trend may reflect changes in reimbursement, it is also possible that it is the result of decreasing satisfaction with available psychosocial therapies. The present study was undertaken to explore the overall effectiveness of these therapies as well as to compare the effects of various components.

**Methods:** A comprehensive literature search identified controlled trials, not necessarily randomized, of psychosocial treatments for primary behavior disorders in children. Eligible studies for the network meta-analysis* were those that reported results using at least 1 of the 3 most common parent-reported outcome measures: the Eyberg Child Behavior Inventory (ECBI) Intensity subscale; the ECBI Problem subscale; or the Child Behavior Checklist Externalizing subscale.
subscale. Interventions were broadly classified as control (treatment as usual or wait-list), treatments with only a child component, those with only a parent component, or multicomponent interventions.

**Results:** A total of 66 studies were included in the systematic review. Of these, 2 examined child-only interventions, 25 parent-only interventions, and 39 multicomponent interventions; 28 of these studies met criteria for inclusion in the meta-analysis. The most common named interventions were the Incredible Years, Parent-Child Interaction Therapy, the Positive Parenting Program, and Multisystemic Therapy.

Child-only, parent-only, and multicomponent interventions were all superior to the control condition. Reductions in disruptive symptom scores were 1.2 standard deviations for both parent-only and multicomponent interventions, compared with 1.0 standard deviation for child-only interventions. The investigators also calculated the probability of each treatment being the most effective. The probability was 43% for both parent-only and multicomponent programs and 14% for child-only programs. However, there was too little evidence to conclude that child-only programs are inferior. Treatment was slightly more effective in preschool children than in older age groups.

**Discussion:** The interventions studied in this meta-analysis were provided in academic settings, and the results may not be generalizable to clinical practice in the community. In addition, the studies did not address concurrent use of medication. As a result, additional study appears to be warranted.


*See Reference Guide.

### Behavioral Activation and Multimodal Treatment

In a randomized controlled trial, SSRI-related activation syndrome hindered the efficacy of cognitive behavioral therapy (CBT) in pediatric obsessive-compulsive disorder (OCD).

**Methods:** Study subjects were 56 children and adolescents, aged 7–17 years, with a primary diagnosis of OCD. Participants received randomized drug therapy with either sertraline (*Zoloft*), titrated on a regular or slow schedule, or placebo. Regular titration was 25–200 mg/day over 9 weeks on a flexible schedule, and slow titration had the same target and duration but proceeded according to fixed increments. The optimal dose was reached at week 4 with regular titration and week 8 with slow titration. After 4 weeks of drug or placebo treatment, all participants began weekly CBT with exposure and response prevention.

SSRI-associated activation was measured using a recently validated scale created by the study research team: the Treatment-Emergent Activation and Suicidality Assessment Profile (TEASAP). This parent-rated instrument consists of 38 items in 5 symptom clusters: irritability; akathisia/hyperkinesis/somatic anxiety; disinhibition/impulsivity; mania; and self-injury/suicidality/harm to others. Scores were classified as low, average, and high, with cutoffs 1 standard deviation above and below the mean. Only activation symptoms that developed during treatment were included in the analysis. Treatment efficacy was assessed using the Children’s Yale-Brown Obsessive Compulsive Scale (CY-BOCS).

**Results:** The average daily sertraline dose was 76 mg for the slow titration group and 148 mg for the regular titration group. Activation symptoms appeared most frequently during the transitions from no treatment to 25 mg/day and from 50 to 75 mg/day. Response, defined as a ≥50% improvement in CY-BOCS score, occurred in 40% of the sample. Activating symptoms
were predictive of a lack of response; response occurred in 74% of those with low levels of acti-
vation symptoms, 37% of those with average levels of activation symptoms, and 5% of those
with high levels of activation symptoms. Fluctuations in activation symptoms were predictive
of fluctuations in OCD symptoms on a session-to-session basis. Among the TEASAP subscales,
OCD symptoms varied in relation to irritability, akathisia, and disinhibition, but not mania
or suicidal ideation. Only variations in irritability predicted OCD symptom outcomes on a
session-to-session basis. Average higher doses of sertraline were associated with lower OCD
symptom severity. However, in a multivariate model, controlling for sertraline dosage did not
affect the relationship between activation symptoms and treatment outcomes.

**Discussion:** Estimates of the incidence of activation symptoms with SSRIs vary widely, in part
because of the lack of a standardized assessment measures. This study is notable as the first to
use such an instrument. The results indicate that activation symptoms, and particularly irri-
tability, may slow treatment gains. Possible reasons include direct negative effects of activation
symptoms on the therapeutic process by disrupting the therapeutic relationship; reducing moti-
vation; increasing disinhibition; or acting via indirect mechanisms such as sleep interference.

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

Reid A, McNamara J, Murphy T, Guzik A, et al: Side-effects of SSRIs disrupt multimodal treatment for pediatric OCD
in a randomized-controlled trial. *Journal of Psychiatric Research* 2015;71 (December):140–147. From the University of
Florida, Gainesville; and other institutions. Funded by the NIMH. Three of the 7 study authors disclosed financial
relationships with commercial sources.

*See Reference Guide.

### Patient Opinions of ECT

Patients with schizophrenia spectrum disorders who had received ECT as adolescents
generally had a positive opinion of the treatment, according to a questionnaire-based study.
Patients with the same disorders who did not receive ECT reported less knowledge about
the treatment, but they did not have negative views of it.

**Methods:** Questionnaires were administered to all available patients with schizophrenia or
schizoaffective disorder who had received treatment with ECT while under age 18 years at a
research hospital in Spain in 2003–12. ECT use was approved by a committee in each case,
according to American Academy of Child and Adolescent Psychiatry (AACAP) guidelines. Of
33 patients who underwent treatment, 19 could be reached and completed the questionnaire
assessing their knowledge, attitude, and experience with ECT. A comparison group of 21
patients, who received antipsychotic medications only, also completed a questionnaire about
general attitudes toward medication.

**Results:** Patients had a mean age of 21 years at the time of assessment. All were outpatients,
most were taking medication, and none was currently receiving ECT. Of the ECT group, 90%
said they currently felt better than they had around the time when they received ECT. Most
patients did not remember the treatment well or at all. Most of them thought they were
receiving ECT to treat their disorder, and none thought it was given as punishment or to
control unacceptable behavior.

Of the 19 patients, 15 (79%) felt that ECT had helped them, 3 did not know or remember, and
1 felt it had not helped; no patient felt it made them worse. About one-third were very scared
before the first ECT session, and almost half felt it was more frightening than having some-
thing done at the dentist. The most commonly reported adverse effects were confusion,
headache, and nausea; 8 patients reported memory problems with ECT, but 5 also reported
memory problems with medication and 4 believed both ECT and medication had improved
their memory. Most patients did not try to hide the fact that they had ECT from others. A total
of 13 patients felt their illness was worse than the ECT treatment, 1 felt ECT was worse, and 4 had no opinion. Patients in the ECT group were more likely than controls to report that ECT was a safe treatment. Most patients in both groups said they would accept ECT in the future if it was recommended.

**Discussion:** AACAP indications for ECT use in adolescents with schizophrenia spectrum disorders are the same as in adults: psychotropic drug resistance, medication intolerance, contra-indication to medication, or a specific clinical indication (e.g., catatonia, neuroleptic malignant syndrome). Although it has been shown to be safe and effective in adolescents, use of ECT in young patients is limited. The limited evidence, however, suggests positive attitudes toward ECT. The positive attitudes of adolescents who undergo ECT could be helpful in counteracting some of the stigma associated with the treatment.

Flamarique I, Castro-Fornieles J, de la Serna E, Pons A, et al: Patients’ opinions about electroconvulsive therapy: what do adolescents with schizophrenia spectrum disorders think? *Journal of Child and Adolescent Psychopharmacology* 2015;25 (October):641–648. From the Hospital Clinic of Barcelona, Spain; and other institutions. Funded by the government of Catalonia; and other sources. Two study authors disclosed financial relationships with commercial sources; the remaining 4 authors declared no competing interests.

### Heart Rate and Violent Criminality

In a Swedish registry-based longitudinal study, low resting heart rate in boys during late adolescence was associated with increased risk of violent criminality, nonviolent criminality, exposure to assault, and unintentional injury in adulthood.¹

**Methods:** Men born in Sweden between 1958 and 1991 who were evaluated at age 18 years for conscription into the country’s military service (mandatory until 2009) comprised the study sample. Blood pressure and resting heart rate were measured as part of the conscription examination, and study subjects were classified into quintiles according to heart rate. The primary outcome was time to first criminal conviction for a crime either violent (e.g., murder, kidnapping, robbery, arson, sexual crimes) or nonviolent (e.g., drug, traffic, property offenses) between 1973 and 2009 (average length of follow-up, 18 years). Secondary outcomes were injuries believed to be the result of fearlessness or stimulation-seeking behavior, and being the victim of an assault. The statistical models were adjusted for a broad spectrum of variables including body size and cardiorespiratory fitness.

**Results:** The cohort consisted of >700,000 men, with an average heart rate of 72 beats per minute (bpm). The lowest quintile had heart rates of <60 bpm. More than 40,000 men were convicted of a violent crime during follow-up. The quintile with the lowest resting heart rate had a statistically significantly elevated risk of all study outcomes compared with every other quintile. (See table.)

For specific types of crime, men in the lowest quintile had a hazard ratio of 1.67 for severe violent crime (i.e., those resulting in imprisonment or other custodial sentences) and 1.42 for less severe violent crime. Rates of sexual crime, however, were not related to heart rate in men who had no other convictions for violent crime. Low heart rate was associated with about a 30–40% increase in each category of nonviolent crime: drug-related, traffic, and property offenses.

| Study outcomes in subjects with the lowest quintile of resting heart rate (35–60 bpm) vs. the highest quintile (reference group, 83–145 bpm). |
|-----------------------------------------------|--------------------------|
| **Outcome**                                | **Hazard Ratio***      |
| Violent crime                               | 1.49                    |
| Nonviolent crime                            | 1.33                    |
| Assault injuries (as victim)                | 1.41                    |
| Unintentional injuries (as victim)          | 1.31                    |
Editorial. Previous studies, with much smaller samples, have shown that low resting heart rate is predictive of antisocial behavior in children and adolescents. The present study firmly establishes the relationship and extends it into adulthood, and suggests that low heart rate may be a marker for broad rule-breaking behavior in general and a predictor of serious violence in particular. Potential explanations for the association include theories that low heart rate is a marker for fearlessness and impulsive stimulation seeking. Persons with these traits may tend to place themselves at risk, increasing their incidence of unintentional injuries and assaults.


2Raine A: Low resting heart rate as an unequivocal risk factor for both the perpetuation of and exposure to violence [editorial]. JAMA Psychiatry 2015;72 (October):962–964. From the University of Pennsylvania, Philadelphia. The author reported no conflicts of interest.

*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.

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.

Network Meta-Analysis: A statistic method that can provide estimates of efficacy for multiple treatment regimens, even when direct comparisons are unavailable. This method extends the traditional meta-analytic technique to allow simultaneous comparisons of the effects of multiple treatments in ≥2 studies that have 1 treatment in common. For example, if in a clinical trial comparing treatment A with treatment B, option A is determined to be superior, and a separate trial in similar patients found option B superior to a third agent, option C, a network meta-analysis of these 2 trials would allow a researcher to conclude that treatment option A is more effective than option C, even though the 2 options have never been directly compared.

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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