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Recommendations for Urine Testing

Urine testing for antipsychotic drugs can be extremely useful in monitoring medication adherence and identifying causes of clinical deterioration, according to an expert consensus of physicians working in community mental health clinics. Despite the inaccuracy of other methods (e.g., patient self-report, clinician estimates) to ascertain adherence in patients with serious mental illness, urine testing in mental health clinics remains uncommon. Urine testing technologies, available since 2013, can test simultaneously for illicit substances and levels of ingested medications, including antipsychotics. Results are available within a few days.

A literature search, focusing on recent articles and reviews, was conducted to identify research on antipsychotic medication. Semi-structured telephone interviews were also conducted with clinicians working in community mental health clinics that used urine drug testing. The interviews evaluated 46 "indications" or hypothetical scenarios, which were grouped into 5 areas: initial evaluation, urine monitoring method, education, feedback, and ongoing treatment. As a third step, a panel of the clinicians with considerable experience with testing rated each of the indications according to appropriateness; impact on treatment, symptoms, and functioning; and feasibility. Items with high ratings by consensus were included in the recommendations.

A total of 15 items, many consisting of combined indications, were highly rated for appropriateness, impact, and feasibility. Urine monitoring at initial intake is recommended for patients with: new symptoms; an established diagnosis of serious mental illness; a risk factor for poor adherence; homelessness; a substance use disorder; or advanced age. Written or verbal education prior to testing is critical and should include a discussion of the importance of adherence, the role of urine monitoring in treatment planning, and any costs the patient might incur. Results should be shared with the patient as soon as possible, and a clinician should be available to discuss concerns. Repeat testing is recommended if there were concerns about a previous result, the patient deteriorates or has an inadequate response,

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or if there is a substantial change in the patient's situation that may require reevaluation. Periodic retesting is recommended, either at set intervals or randomly, and stable patients should be tested annually.

Cohen A, Collins G, Nucifora Jr F, Strobel R, et al: Clinical consensus recommendations for urine testing of adherence to antipsychotics among people with serious mental illness. Psychiatric Services in Advance 2017; doi 10.1176/appi.ps.201700082. From the University of California, Los Angeles; and other institutions. **Funded by Ameritox, Limited. All 6 study authors disclosed financial relationships with commercial sources including Ameritox.**

Adjunctive Cannabinoid for Schizophrenia

Cannabidiol (CBD), a non-intoxicating component of cannabis, reduced positive symptoms when added to background antipsychotic medication in patients with residual symptoms of schizophrenia. The effect was modest but of interest because CBD, unlike antipsychotics, does not appear to work via dopamine receptor antagonism.

Methods: The study was conducted at 15 hospital sites in 3 European countries by the British manufacturer of a CBD product. Participants were 88 adults (mean age, 41 years; 58% men) with a schizophrenia spectrum disorder, partially responsive to antipsychotic medication. Participants were required to have a Positive and Negative Syndrome Scale (PANSS) total score of ≥60 and to be receiving stable antipsychotic medication for ≥1 month. Substance use was not an exclusion criterion, and use of alcohol, marijuana, and other substances was not prohibited during the trial. Participants were randomly assigned to 6 weeks of double-blind treatment with 1000 mg/day CBD, administered in an oral solution in 2 split doses (morning and evening), or placebo. Because this was an exploratory study, there were multiple key efficacy endpoints and additional secondary endpoints.

Results: A total of 83 patients (94%) completed the trial. At baseline, the mean PANSS positive symptom scores were 18 and 17.5 in the CBD and placebo groups, respectively. At 6 weeks, scores were reduced to 14.8 with CBD and to 15.7 with placebo; although the difference was modest, it was statistically significant (p=0.019). Change in the other PANSS domains (i.e., total, negative, and general psychopathology) all favored CBD but fell short of statistical significance. Post-treatment Clinical Global Impression Improvement and Severity scores also differed between the groups. After treatment, more patients who received CBD were rated by their clinician as improved—79% vs 55% (p=0.018)—and the proportion of patients rated as having mild, borderline, or no illness was 45% in the CBD group and 36% in the placebo group (p=0.044). Differences between treatments in the level of functioning and cognitive performance favored CBD but were not statistically significant.

The treatment groups did not differ in prolactin levels, weight, abnormal movements, or any of the other known adverse effects of antipsychotics. Adverse events, mainly gastrointestinal, were generally transient and mild.

Discussion: Previous reports suggest CBD can reduce THC-induced psychosis as well as psychotic symptoms in schizophrenia and Parkinson's disease. Although the effects seen in the present study were modest, they were evident to the treating psychiatrists and were over and above the effects of patients' antipsychotic treatment.

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

McGuire P, Robson P, Cubala W, Vasile D, et al: Cannabidiol (CBD) as an adjunctive therapy in schizophrenia: a multicenter randomized controlled trial. *American Journal of Psychiatry* 2017; doi 10.1176/appi.ajp.2017.17030325. From King's College London, U.K.; and other institutions including GW Pharmaceuticals, Cambridge, U.K. **Funded by GW Research Ltd.; and other sources. Six study authors disclosed financial relationships with commercial sources including GW Pharmaceuticals; the remaining 2 authors declared no competing interests.**

***See Reference Guide.**

Adjunctive Antioxidant for Schizophrenia

In a pilot study, adjunctive low-dose α-lipoic acid (ALA) reduced symptoms of schizophrenia in patients receiving stable antipsychotic medication. ALA is a naturally occurring antioxidant with antiinflammatory actions.

Methods: The trial enrolled 12 patients with chronic schizophrenia, receiving stable doses of antipsychotic medications for at least the previous year. All received 100 mg/day open-label ALA. Schizophrenia symptoms were evaluated using the Brief Psychiatric Rating Scale (BPRS) at baseline and after 4 months of treatment. Response was defined as a ≥25% reduction in BPRS total score. Extrapyramidal symptoms were evaluated with the Simpson-Angus Scale at each monthly visit, and neurocognitive tests were given at entry and after 4 months.

Results: The 10 patients who completed the study had a mean age of 39 years and had been ill for an average of nearly 19 years. All 10 patients met response criteria, showing a mean 64% decrease in the BPRS total score. All symptom dimensions of the BPRS—positive, negative, excitement, and depressive—decreased significantly. Patients also showed improvement in all neurocognitive measures except for verbal fluency. Extrapyramidal symptoms also decreased in severity, and no adverse effects of ALA were observed. There were no changes from baseline in waist circumference, body mass index, complete blood count, or other laboratory variables. There were significant reductions in thiobarbituric acid-reactive substances (TBARS), a marker of lipid peroxidation, and in folic acid.

Discussion: Recent clinical studies, using dosages of 300 or 1200 mg/day, showed no benefit of ALA in patients with schizophrenia. However, older research suggested efficacy with lower dosages. The current findings, although preliminary and requiring replication, support the possibility of a low-dose therapeutic window for ALA in schizophrenia. Randomized trials are needed to confirm the efficacy of adjunctive ALA in schizophrenia.

Sanders L, de Souza Menezes C, Chaves Filho A, de Ameida Viana G, et al: α-Lipoic acid as adjunctive treatment for schizophrenia: an open-label trial. *Journal of Clinical Psychopharmacology* 2017;37 (December):697–701. From the Universidade Federal do Ceara, Brazil; and other institutions. **Funded by the Conselho Nacional de Desenvolvimento Cientifico e Tecnologico, Brazil. The authors declared no competing interests.**

Internet-Based CBT for Bulimia

According to a randomized comparison study, after 1 year, efficacy and cost-effectiveness of internet-based cognitive behavioral therapy for bulimia nervosa are comparable to those of face-to-face therapy. However, over 1 year, out-of-pocket expenses were substantially higher for patients receiving face-to-face therapy.

Methods: A noninferiority trial, conducted at 2 U.S. centers, compared internet-based and face-to-face therapy for bulimia in 179 adults with DSM-IV bulimia nervosa. Both treatments were delivered in a group format, in 16 sessions (90 minutes each) over 20 weeks. Participants traveled to the study sites using personal transportation for face-to-face sessions. Internet therapy was conducted in a text-only online chat format, with anonymous logins and passwords. The primary effectiveness outcome was abstinence from binge eating and purging during the past 28 days, measured with the Eating Disorder Examination, at the end of treatment and at follow-up 1 year from the start of therapy. Cost items included the intervention itself; other health care outside the protocol; and out-of-pocket costs, including software for the internet group and travel time and expenses for face-to-face therapy.

Results: Patients in both groups participated in an average of 8 of the 16 sessions. About 40% completed ≥75% of the sessions. Participants in face-to-face therapy had a higher rate of

binge–purge abstinence immediately after treatment (21% vs 14%), but by 1 year, similar proportions of the 2 groups were abstinent (26% and 30%, respectively). Overall costs of all protocol and non-protocol health care at 1 year were nearly identical for both programs, at slightly more than $4000. However, patients' out-of-pocket expenses were >3-times higher in the face-to-face treatment group, primarily due to travel-related costs. There were no statistically significant differences in the calculated cost-effectiveness of the 2 treatments.

Discussion: Internet-based treatments are often assumed to cost less than face-to-face treatment, but these costs may not be accurately measured in most studies. The lack of difference in cost-effectiveness between internet and face-to-face CBT, along with the convenience and privacy of internet-delivered care, support internet-delivered CBT as a viable option for the treatment of bulimia. Although face-to-face therapy produced faster improvement, abstinence rates increased over time with internet therapy, perhaps because patients had access to online materials that they could continue to review. Accessibility of in-person CBT for bulimia is limited because it is generally provided only by specialized practitioners. Utilizing the internet-based therapy could improve access to care and/or reduce waiting lists for the specialized clinics.

Watson H, McLagan N, Zerwas S, Crosby R, et al: Cost-effectiveness of internet-based cognitive-behavioral treatment for bulimia nervosa: results of a randomized controlled trial. *Journal of Clinical Psychiatry* 2018; doi 10.4088/JCP.16m11314. From the University of North Carolina at Chapel Hill; and other institutions. **Funded by the NIH; and other sources. Six of 14 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

Web-Based Adjunct to Psychotherapy for Depression

In a randomized trial, a web-based program was an effective adjunct to psychotherapy in patients with depression.

Methods: The program, called deprexis, was designed to provide some of the more routine aspects of therapy, mainly psychoeducation and cognitive-based homework. The program consists of 10 modules, covering such areas as cognitive restructuring, behavioral activation, exercise and nutrition, and emotion-focused interventions. Study participants were self-referred patients with unipolar depression and a Beck Depression Inventory-II (BDI-II) score >13. Treatment was provided by licensed therapists using their preferred mode of psychotherapy, with or without the randomly assigned addition of deprexis. All therapists were trained in the program and were free to monitor and support the study patients based on clinical judgment. The primary study outcome was change from baseline in BDI-II score after 12 weeks.

Results: A total of 98 patients were randomly assigned to treatment. More than half had a history of psychotherapy, and more than half were receiving stable antidepressant medication. A total of 69 patients (70%) completed the 12-week assessment, and 44 (45%) participated in follow-up at 6 months. Patients in the active treatment group used the program for >9 hours on average.

After 12 weeks, patients who used deprexis had a significantly greater improvement on the BDI-II than those who did not ($p<0.05$; effect size,* 0.51). The difference was no longer statistically significant at 6 months (effect size, 0.28); however, <50% of patients completed this assessment. Statistically significant effects were also observed on some secondary outcomes: the mental health scale of the Short Form-12 (SF-12; effect size, 1.30; $p<0.05$) and the somatic symptom module of the Patient Health Questionnaire-15 (effect size, 0.58; $p<0.01$). The 2 groups did not differ on other secondary outcome measures, which included the physical subscale of the SF-12 and the Generalized Anxiety Disorder Scale. A total of 16

patients who received deprexis and 9 controls experienced reliable change from baseline in BDI-II score (p=ns); 8 and 2 patients, respectively, had clinically significant improvement on the BDI-II (p=ns). Generally, both clinicians and patients rated the working alliance higher if they received the web-based intervention, but differences were not statistically significant.

Discussion: Although preliminary, the present study results suggest that blending face-to-face psychotherapy with a web-based adjunctive intervention does not have negative effects on the quality of the therapeutic alliance, and that outcomes may actually improve as a result of participation in the online program. The authors note that the lower-than-anticipated sample size may have affected the study's ability to detect effects of more than medium magnitude, as well as potentially explain why significant differences were not detected on some secondary outcome measures.

Editor's Note: Additional information about the deprexis program is available from it's developer, GAIA AG, at https://us.deprexis.com.

Berger T, Krieger T, Sude K, Meyer B, et al: Evaluating an e-mental health program ("deprexis") as an adjunctive treatment tool in psychotherapy for depression: results of a pragmatic randomized controlled trial. *Journal of Affective Disorders* 2018;227 (February):455–462. From the University of Bern, Switzerland; and other institutions. **Funded by the Swiss Natural Science Foundation. The authors did not include disclosure of potential conflicts of interest.**

***See Reference Guide.**

ECT for Dementia-Related Agitation, Aggression

According to a systematic review, ECT could produce clinically significant improvement in severe, resistant agitation and aggression in patients with dementia.

Methods: A comprehensive literature search identified reports of ECT for dementia-related behavior problems published in peer-reviewed journals, regardless of language or study design. Reviewed reports presented original data on patients who received ECT primarily to treat aggression or agitation; mood disorders were permitted but could not be the primary focus of treatment.

Results: The search identified 17 reports (122 patients; age range, 54–98 years), including 1 prospective cohort study with pre- and post-treatment comparisons and 1 case-control study. The remaining reports were retrospective chart reviews, case series, or single case reports. Although many aspects of the studies were not well documented (e.g., measures of cognitive function, concomitant medications, details of the ECT procedure), substantial clinical improvement was reported for 107 of the 122 patients (88%). Improvement often occurred after the second, third, or fourth session. Adverse effects of ECT were generally mild and transient. More severe adverse events were occasionally reported: delirium in 6 patients, seizure in 1, and severe postictal confusion in 2.

The only prospective study reported a statistically significant average improvement of 6 points each on the Cohen Mansfield Agitation Inventory and the Neuropsychiatric Inventory by the 6th ECT session. Most of the patients who improved were noticeably less agitated and aggressive, yelling and screaming stopped, and patients began eating again. Some patients continued to receive psychotropic medication to maintain their response, although at a reduced dose, and others were weaned. Of 82 initial responders for whom follow-up was described, 51 were referred for maintenance ECT.

Discussion: Based on the limited available evidence, ECT appears to be a viable option for treatment of resistant dementia-related agitation and aggression. However, controlled trials

are needed and it will be important to develop treatment guidelines, particularly because most patients who qualify will not be able to provide informed consent.

Study Rating*—16(89%): This study met most criteria for a systematic review; however, the source of funding was not stated.

Van den Berg J, Kruithof H, Kok R, Verwijk E, et al: Electroconvulsive therapy for agitation and aggression in dementia: a systematic review. *American Journal of Geriatric Psychiatry* 2017; doi 10.1016\j.jagp.2017.09.023. From the Parnassia Psychiatric Institute, the Hague, the Netherlands; and other institutions. **Source of funding not stated. The authors declared no competing interests.**

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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.

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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