

EDITOR'S NOTE

This column reflects our commitment to provide you, the primary care physician, with information that will prove helpful in making informed decisions about the care of your patients who suffer from psychiatric disorders. We will highlight abstracts of high interest to you from our sister publication, *The Journal of Clinical Psychiatry*, and summarize pertinent articles from the general scientific literature. We hope that this section is clinically relevant to your practice and that it will encourage you to expand your horizons.

Fluoxetine for the Treatment of Childhood Anxiety Disorders: Open-Label, Long-Term Extension to a Controlled Trial

Clark DB, Birmaher B, Axelson D, et al.

J Am Acad Child Adolesc Psychiatry 2005;44:1263-1270

Objective: To test the effectiveness of fluoxetine for the long-term treatment of anxiety disorders, including generalized anxiety disorder, separation anxiety disorder, and/or social phobia, in children and adolescents.

Method: After completing a randomized, controlled trial (RCT) comparing fluoxetine and placebo, children and adolescents (7-17 years old) with anxiety disorders continued open treatment for 1 year. During this follow-up phase, clinician, parent, and self ratings that included indicators of global severity, global improvement, and anxiety symptoms were employed.

Results: Participants on fluoxetine therapy (N = 42) were compared with those taking no medication (N = 10). Subjects who were taking different medications (N = 4) or who did not complete follow-up (N = 18) were excluded. Significantly better follow-up outcomes on most measures were seen for the fluoxetine group compared with participants taking no medication, including clinician, parent, and self-ratings.

Conclusions: Fluoxetine may be an effective maintenance treatment for children and adolescents with anxiety disorders. Because the follow-up phase was open-label, however, further RCTs are necessary to determine the long-term risks and benefits of fluoxetine for children and adolescents.

Factors That Influence Adolescent Reports of Counseling by Physicians on Risky Behavior

Fairbrother G, Scheinmann R, Osthimer B, et al.

J Adolesc Health 2005;37:467-476

Purpose: To ascertain which factors influence whether low-income adolescents report that their physician discussed risky behavior with them.

Methods: Low-income adolescents in New York City, reached via a random digit-dial survey, were canvassed about depression, smoking, alcohol use, and sexual activity and any screening and counseling received regarding these during health visits.

Results: Based on reports by adolescents surveyed, the prevalence of counseling by physicians was low, and ranged from counseling on depression (17%) to sexually transmitted diseases (52%). In all categories, older adolescents were more apt to be counseled than younger ones. There was a strong association, in bivariate and multivariate models, between having the risk factor and physicians counseling for depression (adjusted OR = 4.42; $p < .001$) and about condom use (adjusted OR = 4.06; $p < .01$) and birth control (adjusted OR = 2.76; $p < .03$). Nevertheless, many adolescents engaging in risky behavior had failed to receive counseling. Many adolescents have not received a private and confidential consultation with their physician, which was associated with receiving counseling.

Conclusions: By their own admission, adolescents are receiving less than adequate counseling on risks and risky behavior. It is necessary to improve how counseling is obtained and to make certain that adolescents receive private and confidential visits.

Long-Term Weight Gain in Patients Treated With Open-Label Olanzapine in Combination With Fluoxetine for Major Depressive Disorder

Andersen SW, Clemow DB, Corya SA

J Clin Psychiatry 2005;66:1468-1476

Objective: Patients with major depressive disorder (MDD) treated with olanzapine in combination with fluoxetine (OFC) demonstrate robust improvement in their depressive symptoms. Treatment with olanzapine may impact a patient's weight; thus, long-term weight gain and potential predictors (e.g., age and gender) and correlates (e.g., cholesterol and glucose levels) of weight gain were investigated in OFC-treated patients with MDD.

Method: Outpatients who met the DSM-IV diagnostic criteria for MDD were included (N = 549) in the current analyses of this 76-week, open-label study (February 2000 to July 2002). Maximum, endpoint, and potentially clinically significant (PCS; $\geq 7\%$ increase from baseline) weight gain; time to PCS weight gain; and predictors and correlates of weight change were assessed. Patients were treated once daily with oral olanzapine (6, 12, or 18 mg) plus fluoxetine (25, 50, or 75 mg) capsules. Statistical significance for all tests was based upon $p \leq .05$.

Results: Mean baseline-to-endpoint weight change was 5.6 ± 6.6 kg (12.3 ± 14.6 lb). Weight gain plateaued by 52 weeks. Fifty-six percent of patients met criteria for PCS weight gain by 76 weeks, and the median time to PCS weight gain was 16 weeks. Low baseline body mass index (BMI), female gender, younger age, and increased fluoxetine dose were predictors of weight gain; olanzapine dose was not. Patients with early (≤ 6 weeks) rapid PCS weight gain were 4.6 times more likely to gain substantial ($\geq 15\%$) weight long-term (weeks 7–76). Changes to endpoint in total cholesterol and systolic blood pressure values were positively correlated with weight change.

Conclusion: Long-term (76 weeks) OFC treatment may lead to a large percentage (56%) of patients meeting criteria for PCS weight gain ($\geq 7\%$). The risk of weight gain may be significantly increased for OFC-treated patients who have a low BMI or who are female, younger, or taking high-dose fluoxetine. It is important that prescribers balance the risk of weight gain with the benefit of treatment for individual patients with depression.

Cognitive Therapy and Exposure in Vivo Alone and in Combination With Fluvoxamine in Obsessive-Compulsive Disorder: A 5-Year Follow-Up

van Oppen P, van Balkom AJ, de Haan E, et al.

J Clin Psychiatry 2005;66:1415–1422

Background: Information regarding the long-term effectiveness of the combination of pharmacotherapy and cognitive-behavioral therapy (CBT) in the treatment of obsessive-compulsive disorder (OCD) is limited. Our study is the first to examine the long-term effectiveness of cognitive therapy (CT) and to compare long-term effectiveness of CT alone, exposure in vivo with response prevention (ERP) alone, and CBT (either CT or ERP) in combination with fluvoxamine in the treatment of OCD.

Method: Of 122 outpatients with primary DSM-III-R–defined OCD originally enrolled in 2 randomized controlled trials, 102 patients (45 male/57 female; mean \pm SD age = 36.2 ± 10.7 years; range, 19–64 years) were available to be assessed for the presence and severity of OCD and comorbid psychopathology at follow-up. Follow-up data were collected from November 1996 to June 1999.

Results: After 5 years, 54% of the participants no longer met the DSM-III-R criteria for OCD. Long-term outcome did not differ between the 3 treatment groups. At follow-up, treatment dropouts appeared to have more severe OCD complaints compared with treatment completers. Compared with patients receiving CT alone, significantly ($p < .005$) more patients receiving CBT with fluvoxamine used antidepressants 5 years later.

Conclusions: This study demonstrates that at 5-year follow-up (1) prevalence of OCD had declined in all 3 treatment conditions, (2) the clinical benefits of all 3 treatment conditions were maintained, (3) OCD complaints were more severe for treatment dropouts than for treatment completers, and (4) about

half of the patients initially treated with fluvoxamine continued antidepressant use.

Cost-Effectiveness of Improving Primary Care Treatment of Late-Life Depression

Katon WJ, Schoenbaum M, Fan MY, et al.

Arch Gen Psychiatry 2005;62:1313–1320

Context: Depression is a leading cause of functional impairment in elderly individuals and is associated with high medical costs, but there are large gaps in quality of treatment in primary care.

Objective: This study sought to assess the incremental cost-effectiveness of the Improving Mood Promoting Access to Collaborative Treatment (IMPACT) collaborative care management program for late-life depression.

Design, Setting, and Participants: This randomized controlled trial was sited at 18 primary care clinics from 8 health care organizations in 5 states. Patients were recruited from July 1999 to August 2001. The sample consisted of a total of 1801 patients 60 years or older with major depression (17%), dysthymic disorder (30%), or both (53%).

Intervention: Patients were randomly assigned to the IMPACT intervention (N = 906) or to standard primary care (N = 895). Access to a depression care manager supervised by a psychiatrist and primary care physician was provided to intervention patients. Education, support of antidepressant medications prescribed in primary care, and problem-solving treatment in primary care (a brief psychotherapy) were made available by depression care managers.

Main Outcome Measures: Total outpatient costs, depression-free days, and quality-adjusted life-years.

Results: Intervention patients experienced 107 (95% confidence interval [CI] = 86 to 128) more depression-free days over 24 months compared with patients who received standard care. Total outpatient costs were USD \$295 (95% CI = $-\$525$ to $\$1115$) higher during this period. The incremental outpatient cost per depression-free day was USD $\$2.76$ (95% CI = $-\$4.95$ to $\$10.47$), and incremental outpatient costs per quality-adjusted life-year ranged from USD $\$2519$ (95% CI = $-\$4517$ to $\$9554$) to USD $\$5037$ (95% CI = $-\$9034$ to $\$19,108$). Results of a bootstrap analysis suggested a 25% probability that the costs of the IMPACT intervention were lower and that the intervention was more effective (i.e., was “dominant”) than standard care.

Conclusions: The IMPACT intervention represents a high-value investment for older adults as it is associated with high clinical benefits at a low increment in health care costs.

Cognitive-Behavioral Therapy for Management of Anxiety and Medication Taper in Older Adults

Gorenstein EE, Kleber MS, Mohlman J, et al.

Am J Geriatr Psychiatry 2005;13:901–909

Objective: To compare the reduction in medication use and improvement in psychological symptoms in patients with late-life anxiety receiving cognitive-behavioral therapy with adjunctive medical management for medication taper (CBT-MM) with that in a control group receiving only medical management (MM).

Methods: Forty-two patients (aged > 60 years) seeking to decrease their use of anxiolytic medication were assigned to 1 of 2 groups (CBT-MM or MM), through a randomization plus

difference-minimization process (in order to equate for medication use).

Results: Medication use was significantly decreased in patients who completed the CBT-MM protocol, although not at a greater rate than patients who completed the MM assignment. Still, significantly greater amelioration of psychological symptoms was seen for patients who completed the CBT-MM protocol had compared with those patients who completed the MM protocol. Although some improvements remained evident at 6-month follow-up, not all did. Treatment effects were similar for the intent-to-treat and completer analyses but were stronger for the completers.

Conclusion: Psychological symptoms in elderly patients with anxiety can be ameliorated by cognitive-behavioral therapy while those patients reduce anxiolytic medication.

Depression and Role Impairment Among Adolescents in Primary Care Clinics

Asarnow JR, Jaycox LH, Duan N, et al.

J Adolesc Health 2005;37:477-483

Purpose: To assess the relationship between depression and role impairment in a cohort of adolescents drawn from a primary care sample, with and without considering the consequences of medical comorbidity.

Method: Cross-sectional audit of sequential primary care patients, 13 to 21 years old (N = 3471), selected from 6 sites including public health, managed care, and academic health center clinics. Likely instances of depressive disorder, depressive symptoms, and routine medical complaints were examined through a brief self-report screening questionnaire. Two signs of role impairment were used as the main outcome measures: (1) decrease in productivity/role activity, defined as not in school or working full time; and (2) low educational attainment, defined as more than 2 years behind in school or 20 years or older and failed to complete high school.

Results: Adolescents whose screening results indicated a likely depressive disorder had higher rates of decreased productivity/role activity (19% vs. 13%; OR = 1.69; 95% CI = 1.39 to 2.06; $p < .001$) and low educational attainment (20% vs. 15%; OR = 1.47; 95% CI = 1.21 to 1.78; $p < .001$). After controlling for the effect of a general medical condition, probable depressive disorder was a unique predictor of these impairment indicators. The presence of a general medical condition did not contribute to role impairment when depression was controlled for.

Conclusions: Positive screening results for depression in adolescent primary care patients predict impairment in school/work productivity and educational attainment. These results highlight the important role of primary care clinicians in noting depression and role limitations in this group of patients.

Misdiagnosed Patients With Bipolar Disorder: Comorbidities, Treatment Patterns, and Direct Treatment Costs

Matza LS, Rajagopalan KS, Thompson CL, et al.

J Clin Psychiatry 2005;66:1432-1440

Objective: The purpose of this study was to examine comorbidities, treatment patterns, and direct treatment costs of patients with bipolar disorder who are misdiagnosed with unipolar depression.

Method: This study is a retrospective analysis of data from the MarketScan Commercial Claims and Encounters (CCE)

database. Logistic regressions and analyses of variance were used to compare the misdiagnosis cohort to 3 age- and gender-matched comparison cohorts (recognized bipolar, depression, and no psychiatric disorders based on ICD-9-CM criteria) during the year 2000.

Results: Each cohort had 769 individuals (68.0% female; mean age of roughly 42 years). The misdiagnosis cohort had higher rates of several psychiatric comorbidities than the depression cohort (e.g., personality disorders, alcohol abuse, psychotic disorder) and the bipolar cohort (e.g., generalized anxiety disorder, panic) but a lower rate of psychotic disorders than the bipolar cohort ($p < .05$). Compared with the bipolar cohort, the misdiagnosis cohort was more likely to receive antidepressants, but less likely to receive anticonvulsants, antipsychotics, or lithium (all p values $< .001$). Antidepressant rates were similar among the misdiagnosis and depression cohorts. Group differences were found in respective mean annual costs for anticonvulsants, antipsychotics, lithium, antidepressants, and total treatment costs: bipolar (USD \$442, \$310, \$67, \$497, \$8600); misdiagnosis (USD \$221, \$185, \$20, \$704, \$8761); depression (USD \$70, \$74, \$5, \$657, \$7288).

Conclusion: Misdiagnosed bipolar patients received inappropriate and costly treatment regimens involving overuse of antidepressants and underuse of potentially effective medications. Patterns of psychiatric comorbidity suggest one possible strategy for improving recognition of bipolar disorder among patients presenting with depressive symptoms. Patients who present with the observed pattern of comorbidities may benefit from additional screening for bipolar disorder. It is recommended that steps be taken to minimize misdiagnosis in clinical settings.

Escitalopram in the Treatment of Depressed Elderly Patients

Kasper S, de Swart H, Friis Andersen H

Am J Geriatr Psychiatry 2005;13:884-891

Objective: An important medical challenge is the management of depression in elderly patients, and additional clinical studies are necessary. Efficacy and tolerability of escitalopram and fluoxetine were compared with placebo for major depressive disorder (MDD) in elderly patients.

Methods: In an 8-week, randomized, double-blind trial, escitalopram (10 mg/day) and fluoxetine (20 mg/day) were compared with placebo in elderly patients with MDD. Efficacy was measured by the change from baseline in mean Montgomery-Asberg Depression Rating Scale (MADRS) total score at endpoint, using the last observation carried forward.

Results: The intent-to-treat cohort consisted of 517 patients, with 173 patients in the escitalopram group, 164 patients in the fluoxetine group; and 180 patients in the placebo group. The mean age of patients was 75 years (range, 65-93 years). Neither active treatment was superior to placebo; therefore, this was a "failed study," and results should be interpreted with appropriate caution. Fluoxetine was significantly less efficacious than both escitalopram and placebo, which were not significantly different from each other, according to the primary efficacy measure. Patients in the placebo group withdrew at a rate of 2.8% due to adverse events and 4.4% due to lack of efficacy. Patients in the escitalopram group withdrew at rates of 9.8% and 1.7%, respectively, and withdrawal rates for patients taking fluoxetine were 12.2% and 1.8%, respectively. Among patients in the escitalopram group, no single adverse event occurred at an incidence of 10% or greater.

Conclusions: While both escitalopram and fluoxetine were well tolerated by elderly patients with MDD in this trial, neither medication showed efficacy greater than placebo.

Does the Geriatric Depression Scale Distinguish Between Older Adults With High Versus Low Levels of Suicidal Ideation?

Heisel MJ, Flett GL, Duberstein PR, et al.

Am J Geriatr Psychiatry 2005;13:876–883

Objective: Although the Geriatric Depression Scale (GDS) is frequently used to screen for late-life depression, it fails to directly evaluate thoughts of death or suicide. The authors investigated whether 30-item (GDS) and 15-item (GDS-SF) GDS scales distinguish between older adults with high versus low levels of suicidal ideation.

Methods: 105 adults, 65 years or older, were enrolled in a cross-sectional study through medical and psychiatric inpatient and outpatient practices, nursing and retirement residences, and community-based seniors' programs.

Results: GDS scores showed a positive association with self-report and clinician-administered measures of suicidal ideation. Groups high or low in self-reported suicidal ideation were identified by 15 of 30 GDS items and 7 of 15 GDS-SF items. Criterion validity were indicated for the GDS measures with respect to suicidal ideation at cut-off scores of 12 for the GDS and 6 for the GDS-SF. Five internally consistent GDS items, assessing hopelessness, worthlessness, emptiness, an absence of happiness, and absence of the perception that it is "wonderful to be alive," were highly associated with suicidal ideation.

Conclusion: Older patients at risk for suicide may be identified through screening with the GDS and GDS-SF, although clinicians are advised to further evaluate the risk of suicide using measures particularly designed to determine the presence and severity of suicidal ideation.

Residual Symptoms in Depressed Patients After Treatment With Fluoxetine or Reboxetine

Nelson JC, Portera L, Leon AC

J Clin Psychiatry 2005;66:1409–1414

Background: Residual symptoms are common and have a variety of consequences in depressed patients who respond to treatment, but seldom have specific residual symptoms been assessed. We examined the frequency and severity of residual depressive symptoms in 2 studies comparing the selective serotonin reuptake inhibitor (SSRI) fluoxetine with the norepinephrine reuptake inhibitor (NRI) reboxetine.

Method: Data from two 8-week, previously published, double-blind, random-assignment studies comparing fluoxetine and reboxetine were obtained. Both studies included men and women who met DSM-III-R criteria for unipolar nonpsychotic major depression. Symptoms were assessed with the 21-item Hamilton Rating Scale for Depression (HAM-D). The frequency and severity of residual symptoms were determined in the patients who completed treatment and responded (had at least 50% improvement on the HAM-D).

Results: In study 1, 117 patients completed treatment and responded. In study 2, 113 patients completed treatment and responded. The most frequent symptoms present after treatment were psychic anxiety, lack of interest, somatic anxiety, and depressed mood. No residual symptom differed significantly

between treatment groups in both samples. Ordinal logistic regression, used to control for baseline symptom severity, revealed no other differences between drug groups except that decreased libido was significantly greater with fluoxetine in study 1 and study 2. Three composite scores for residual anxiety, sleep disturbance, and reduced drive did not differ between drug groups.

Conclusion: This study found no differences in residual symptoms in depressed patients who responded to treatment with the SSRI fluoxetine and the NRI reboxetine, with the exception that the fluoxetine group had a greater decrease in sexual interest, a likely side effect of that drug.

Cost-Effectiveness of an Intervention to Prevent Depression in At-Risk Teens

Lynch FL, Hornbrook M, Clarke GN, et al.

Arch Gen Psychiatry 2005;62:1241–1248

Contact: Children of depressed parents often suffer from depression as teenagers. Prevention strategies are available, but the balance of their incremental costs and benefits will determine their use.

Objective: To determine the incremental cost-effectiveness of a group cognitive-behavioral program to prevent depression in teenaged offspring of depressed parents.

Method: A cost-effectiveness analysis of a recent randomized, controlled trial was conducted at Kaiser Permanente Northwest, a large health maintenance organization. Teenagers (aged 13 to 18 years) deemed susceptible to depression received standard care (N = 49) or standard care plus a 15-session group cognitive therapy prevention program (N = 45). Depression-free days and quality-adjusted life-years were interpreted from clinical results. The analysis comparing the intervention with usual care for 1 year after the intervention combined total health maintenance organization costs, costs of services received elsewhere, and family costs with clinical outcomes.

Results: In the intervention group, total direct and indirect costs increased by \$610, and the intervention cost was, on average, \$1632. A possible cost offset is suggested, however, in that the result was not statistically significant. In the base-case analysis, incremental cost per depression-free day was estimated at \$10 (95% CI = -\$13 to \$52) or \$9275 per quality-adjusted life-year (95% CI = -\$12,148 to \$45,641).

Conclusions: A brief program aimed at preventing depression in children of depressed parents has a favorable cost-effectiveness profile when compared with that of standard depression therapies and other health interventions commonly provided for in insurance contracts.

Sertraline Versus Fluvoxamine in the Treatment of Elderly Patients With Major Depression: A Double-Blind, Randomized Trial

Rossini D, Serretti A, Franchini L, et al.

J Clin Psychopharmacol 2005;25:471–475

Background: Major depression is a common diagnosis in the elderly population. Tricyclic antidepressants have long-established effectiveness, and the efficacy of selective serotonin reuptake inhibitors appears to be comparable, with increased tolerability and safety. Because there is a paucity of data concerning fluvoxamine in the treatment of depression in the elderly population, the authors sought to compare its

efficacy and tolerability with those of sertraline in a sample of elderly patients.

Method: In this double-blind, randomized trial, 93 hospitalized patients older than 59 years, meeting DSM-IV criteria for a major depressive episode, were given sertraline (150 mg/day) or fluvoxamine (200 mg/day) for a period of 7 weeks. A reduction on the Hamilton Rating Scale for Depression score to 8 or below was considered a clinical response.

Results: The response rates were 55.6% (25/45) and 71.8% (28/39) for sertraline and fluvoxamine, respectively, at study's end. Differences in final response rates between the 2 treatment groups were not significant ($p = .12$). A significant difference in the decrease of depressive symptoms between the 2 treatment groups, favoring fluvoxamine, was disclosed by a repeated-measures analysis of variance on the Hamilton Rating Scale for Depression scores ($p = .007$). There was no difference in the overall safety profile of sertraline and fluvoxamine, which was favorable for both medications.

Conclusion: This double-blind trial indicates that sertraline and fluvoxamine may be effective in the treatment of elderly depression, with some advantage in terms of speed of response for fluvoxamine. Further placebo-controlled studies are necessary to replicate these findings.

Risk of Death in Elderly Users of Conventional vs. Atypical Antipsychotic Medications

Wang PS, Schneeweiss S, Avorn J, et al.

N Engl J Med 2005;353:2335-2341

Background: An advisory warning was recently issued by the U.S. Food and Drug Administration (FDA) stating that atypical antipsychotic medications increase mortality among

elderly patients. Typical antipsychotics were not included in the advisory, however, and the risk of death with these older medications is unknown.

Methods: This retrospective cohort study examined 22,890 patients 65 years or older with drug insurance coverage in Pennsylvania who were prescribed a typical or atypical antipsychotic medication between 1994 and 2003. The risk of death within 180 days, less than 40 days, 40 to 79 days, and 80 to 180 days after initiation of therapy with an antipsychotic medication was compared using analyses of mortality rates and Cox proportional-hazards models. Traditional multivariate Cox models, propensity-score adjustments, and an instrumental-variable analysis were used to control for potential confounding variables.

Results: A significantly higher adjusted risk of death was associated with typical antipsychotics than with atypical antipsychotics at all intervals studied (≤ 180 days: RR = 1.37; 95% CI = 1.27 to 1.49; < 40 days: RR = 1.56; 95% CI = 1.37 to 1.78; 40 to 79 days: RR = 1.37; 95% CI = 1.19 to 1.59; and 80 to 180 days: RR = 1.27; 95% CI = 1.14 to 1.41) and in all subgroups classified according to the presence or absence of dementia or nursing home residency. The highest risk increases took place shortly after initiation of therapy and with higher dosages of typical antipsychotics. Analyses performed with the use of propensity-score adjustment and instrumental-variable estimation confirmed the heightened risks associated with typical as compared with atypical antipsychotics.

Conclusions: Although preliminary, these findings suggest that typical antipsychotics are as likely or more likely to increase the risk of death among elderly persons as the atypicals and that atypical antipsychotics that are discontinued because of the FDA advisory should not be replaced by conventional antipsychotics.