DEPRESSION:
Mind and Body

Advances in the Understanding and Treatment of Depression and its Physical Symptoms

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The Metabolic Syndrome and Depression: A Review
John W Goethe, Bonnie L Szarek, and Charles F Caley

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The Benefits of Exercise for Mood Disorders
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Meeting Report
The 20th ECNP Annual Congress

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Clinical Reviews
Treatment Strategies 166
Epidemiology 170
Pathogenesis 172
Comorbidities 172
Prognosis 173

Meeting Report
The 20th European College of Neuropsychopharmacology (ECNP) Annual Congress, Vienna, Austria 178
The Metabolic Syndrome and Depression: A Review

John W Goethe, MD¹, Bonnie L Szarek, RN¹, and Charles F Caley, PharmD¹²

¹Burlingame Center for Psychiatric Research and Education, Institute of Living, Hartford; and ²University of Connecticut School of Pharmacy, Storrs, CT, USA

The metabolic syndrome (MetS) is a cluster of conditions associated with an increased risk of cardiovascular disease, morbidity, and mortality. Most studies of this syndrome in psychiatric populations point to its association with schizophrenia and atypical antipsychotics. Recent data suggest that patients with depression are also at a high risk of MetS. This article reviews studies of the prevalence of MetS in patients with depression, along with the available data concerning the medication and demographic variables associated with MetS. Studies to date indicate that the prevalence of MetS in depression is much greater than that reported for the general North American population (36–57.9% vs. 26.7%) and is similar to the rate found in outpatients with schizophrenia (40.9%). There is a clear need for routine monitoring of depressed patients to ensure early detection of any of the MetS criteria. These metabolic measures appear to be inter-related, and intervention when only one is present may prevent progression to the full syndrome. Depression: Mind and Body 2008;3(4):138–49.

A number of metabolic conditions, often occurring in clusters, have long been associated with an increased risk of cardiovascular disease (CVD), morbidity, and mortality [1,2]. For nearly a century a variety of names have been applied to a clinical picture that is now known as “the metabolic syndrome” (MetS) [3]. This term is widely accepted, but there is ongoing debate about the most appropriate definition for this syndrome. At present there are at least six definitions of MetS (summarized in Table 1) but, despite substantive differences in the individual criteria applied, there is agreement that obesity, hypertension, and alterations in glucose and lipid metabolism are the critical CVD risk factors [4–13].

The consequences of these alterations in metabolic status have been described in the general medical setting for many years. MetS has been recognized as a significant problem in psychiatric patients in the past few years [14], but the studies that have examined metabolic disturbances in psychiatric populations have focused primarily on the association of MetS with schizophrenia and with atypical antipsychotics [15]. Recent data show that patients with depression are also at a high risk of MetS [16–20].

This paper reviews the English language literature addressing the prevalence of MetS in depression, and the medication and demographic variables associated with this syndrome. However, it is important from a patient care perspective to be aware of the implications of any metabolic finding, and this review also includes reported associations with any of the individual components of MetS (i.e., high body fat, glucose/insulin dysregulation, dyslipidemia, and hypertension). Studies were identified using MEDLINE with the keywords “depression” or “major depressive disorder” (MDD) between January 2000 and September 2007 and with the keywords “antidepressants” (as a drug category and for each individual antidepressant) from January 1959 to September 2007, in combination with any of the following terms: metabolic syndrome, glucose, diabetes mellitus, obesity, dyslipidemia, and hypertension. All of the citations in the identified articles were also reviewed.

Prevalence of MetS in patients with depression

In contrast to the literature on MetS in schizophrenia, few studies have sought to determine the prevalence of this condition (i.e., the “syndrome” as defined over the past decade) in patients with depression. In a study of 121 outpatients with longstanding MDD diagnosis based on the Structured Clinical Interview for the DSM-IV, 36% met the National Cholesterol Education Program’s Adult Treatment Panel III (ATP-III) criteria for MetS [17], a rate higher than that reported for the general population (26.7%) [21], but similar to that found in outpatients with schizophrenia (40.9%) [22]. Furthermore, at 6-year follow-up the...
Table 1. Metabolic syndrome criteria.

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<td><strong>Body fat</strong></td>
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<tr>
<td>BMI &gt;30 kg/m² and/or WHR &gt;0.90 in men/WHR &gt;0.85 in women</td>
<td>✓</td>
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<td>WC ≥94 cm in men or ≥80 cm in women</td>
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<td>WC ≥102 cm in men or ≥88 cm in women</td>
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<td>✓</td>
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<td>BMI &gt;25 kg/m²</td>
<td>✓</td>
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<td>Increased WC (population-specific)</td>
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<td><strong>Dyslipidemia</strong></td>
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<td>TG ≥150 mg/dL and/or HDL &lt;35 mg/dL in men or &lt;39 mg/dL in women</td>
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<td>TG ≥150 mg/dL and/or HDL &lt;39 mg/dL in men or women</td>
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<td>✓</td>
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<tr>
<td>TG ≥150 mg/dL and/or HDL &lt;40 mg/dL in men or &lt;50 mg/dL in women</td>
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<td>TG ≥150 mg/dL and/or HDL &lt;40 mg/dL in men or &lt;50 mg/dL in women</td>
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<td>TG ≥150 mg/dL or TG medication and/or HDL &lt;40 mg/dL in men or &lt;50 mg/dL in women</td>
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<td><strong>Blood pressure</strong></td>
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<td>≥140/90 mmHg</td>
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<td>≥140/90 mmHg or hypertension medication</td>
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<td>≥130/85 mmHg</td>
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<td>≥130 mmHg systolic or ≥85 mmHg diastolic or hypertension medication</td>
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<td><strong>Glucose dysregulation</strong></td>
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<td>IGT, IFG, or T2DM</td>
<td>✓</td>
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<tr>
<td>IGT or IFG (but not DM)</td>
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<td>FBS &gt;110 mg/dL (includes DM)</td>
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<td>✓</td>
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<td>FBS ≥100 mg/dL (includes DM)</td>
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<td>FBS ≥100 mg/dL or medication for elevated glucose</td>
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<td><strong>Insulin resistance</strong></td>
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<tr>
<td>IGT, IFG, T2DM, or ↓ insulin sensitivity</td>
<td>✓</td>
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<td>Plasma insulin &gt;75th percentile</td>
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<tr>
<td>IGT or IFG</td>
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<td><strong>Other</strong></td>
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<td>Microalbuminuria</td>
<td>✓</td>
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<td>Other features of insulin resistance</td>
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</table>

1. any three in this column; 2. required, plus any two in this column; 3. required, plus ≥1 in this column based on clinical judgment; 4. if both TG and HDL are positive, counts as two criteria; 5. family history of T2DM, polycystic ovary syndrome, sedentary lifestyle, advancing age, ethnic group susceptible to T2DM; AACE: American Association of Clinical Endocrinologists; AHA/NHLBI: American Heart Association and National Heart, Lung, and Blood Institute; ATP-III: National Cholesterol Education Program Adult Treatment Panel III; BMI: body mass index; DM: diabetes mellitus; EGIR: European Group for Study of Insulin Resistance; FBS: fasting blood sugar; HDL: high-density lipoprotein cholesterol; IDF: International Diabetes Foundation; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; T2DM: type 2 diabetes mellitus; TG: triglyceride; WC: waist circumference; WHO: World Health Organization; WHR: waist to hip ratio.
prevalence of MetS in the MDD sample had increased among those still meeting criteria for a current episode of MDD compared with those who were no longer depressed (57.9% vs. 32.4%, respectively).

Among patients with MDD, certain subgroups may be at an increased risk of MetS. In one inpatient sample, individuals aged ≥40 years (odds ratio [OR] 3.72, 95% confidence interval [CI] 2.37–6.17), females (OR 2.00, 95% CI 1.26–3.17), and Latinos (OR 1.99, 95% CI 1.21–3.29) were approximately 2–4 times more likely to have MetS [19]. Severity of illness may also increase the risk of MetS. Räikkönen et al.’s study of 425 female outpatients showed that subjects with higher baseline Beck Depression Inventory scores were more likely to have MetS at follow-up than those with lower scores (hazard ratio 1.29, CI 1.03–1.62) [23].

A number of investigators have reported associations between depression and various medical conditions, some of which are relevant to MetS. In a recent review of this literature, Brown and colleagues concluded that depression is associated with increased risks of obesity, hypertension, and diabetes, but not of hyperlipidemia [24]. Thus some, but not all, MetS criteria are common in MDD patients [17]. The next section summarizes the reported associations between depression and each criterion of MetS.

**MetS criteria and depression**

**Body fat criterion**

The lack of consensus about MetS measures is particularly evident in the measurement of body fat. For example, ATP III uses waist circumference (WC) [10] while the World Health Organization (WHO) uses body mass index (BMI) [8] or waist/hip circumference ratio, differences that can affect the reported prevalence of this criterion and rates of MetS [18]. There is agreement that the measurement of interest is visceral adiposity (also referred to as central obesity), but the gold standard metric would involve tests such as abdominal magnetic resonance imaging, which are neither practical in the general clinical setting nor typically used in the studies published to date.

The obesity–depression literature is extensive, reaching back several decades, but largely without specific reference to a “syndrome” of multiple metabolic findings. McElroy et al. published a comprehensive review in 2004 and proposed a model that emphasizes the complex inter-relationships between obesity and mood disorders [25]. Subsequently, published data (summarized in Table 2) have further supported the association between depression and one or more of the commonly used measures of body fat. One of these studies, using the ATP III criteria, found increased WC in 43.8% of inpatients with a clinical diagnosis of MDD; increased WC was associated with age ≥40 years (OR 1.91, 95% CI 1.39–2.61) and female gender (OR 4.46, 95% CI 3.22–6.18) [19]. Conversely, several authors have noted that individuals meeting this MetS criterion are more likely to have depression (whether lifetime or current) and to respond more slowly and less robustly to antidepressants [32].

**Glucose/insulin dysregulation**

Measures of glycemic control also vary (Table 1). Some authorities, for example, require direct assessment of insulin resistance while others use a broader definition of dyscontrol (e.g., fasting blood sugar [FBS] ≥100 mg/dL).

There is an extensive literature concerning diabetes and depression, documenting both a high rate of depression in patients with diabetes mellitus (see review by Katon et al. [33]) and an increased likelihood of developing type II diabetes in patients with depression (see review by Musselman et al. [44]). Table 3 provides a summary of studies from 2003 to the present day. Using pooled data, Kinder et al. recently estimated that the risk of a future diagnosis of diabetes is 37% greater in depressed than in non-depressed individuals [45]. Heikskan et al. found that 48% of 149 depressed outpatients in a longitudinal study were hyperglycemic at 6-year follow-up [17].

A number of studies suggest a link between depression and insulin resistance [17,20,26,36,37,40,42,46–48], but these associations could be due to a common underlying etiology or to lifestyle and behavioral patterns.

It is of interest that resolution of depressive symptoms may lead to improvements in glycemic control. For example, Okamura described three non-diabetic depressed patients whose abnormalities in glucose tolerance, insulin secretion, and insulin sensitivity resolved with recovery from the depressive episode, even though they had no change in weight [47]. Similarly, Weber-Hamann and colleagues found that in 89 diabetes patients with MDD, insulin sensitivity improved after successful treatment with antidepressants [49]. These results are consistent with several studies by Lustman et al. [50–53] but not with another recent investigation [54].

**Dyslipidemia criterion**

As noted before, a recent review concluded that depression does not appear to be associated with hyperlipidemia [24]. Supporting this view are two studies reporting that the proportion of patients meeting the ATP III triglyceride and high-density lipoprotein (HDL) criteria for MetS was 30% (36 of 121) and 23% of males and 37% of females, respectively, in a sample of chronically ill depressed outpatients [17], and 32.7% (200 of 611) and 37.8% of subjects, respectively, in a sample of inpatients with MDD [19]. These rates are similar to those found in community samples, with hypertriglyceridemia present in
30.2% and low HDL levels found in 37.9% [21]. Furthermore, in a study of patients with diabetes, the odds of meeting American Diabetes Association criteria for hypercholesterolemia were no greater for those with a mood disorder or schizophrenia than for those in the non-psychiatrically ill group [55]. However, there are data that suggest a specific association between depression and low total cholesterol [56–67].

There may be an association between dyslipidemia and treatment response in patients with depression. Sonowalla and colleagues found that depressed patients with elevated cholesterol levels were significantly more likely to be non-responders to fluoxetine [68], and that patients with treatment-resistant depression had higher triglyceride levels at baseline compared with responders [69].

### Blood pressure

The deleterious effects of hypertension on cardio- and cerebrovascular health are well established, but it is difficult to draw conclusions about MetS prevalence from this literature as elevated blood pressure is variably defined. A lower blood pressure value is used to meet this criterion in the ATP III compared with the WHO definition of MetS (Table 1). Some, but not all, studies use a diagnosis of hypertension or current receipt of an antihypertensive medication as equivalent to having a recorded blood pressure greater than the specified cut-off point. In addition, as illustrated in Heiskanen et al.’s study of chronically depressed outpatients, the proportion of patients with hypertension (ATP III criteria) can vary depending on the use of the systolic (76%) versus diastolic measure (57%) [17]. Nonetheless, it seems clear that the prevalence of an elevated blood pressure is greater in depressed patients compared with community samples (32.2%) [21]. Depressed patients are also at an increased risk of hypertension, based on the Baltimore Catchment Area study (OR 2.16, 95% CI 0.94–4.98) [70]. The largest risk factor in this study was being aged 50–64 years at baseline (OR 2.16), although in another study of late-life depression, hypertension was not associated with depression [42]. Depressed men aged 71–89 years had higher rates of diabetes (23.1% vs. 13.2%) and elevated triglycerides (32.1% vs. 20.9%) but not hypertension (49.0% vs. 46.1%) when compared with non-depressed individuals. In 2005, a review concluded that the relationship between depression and hypertension is

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**Table 2. Associations between body fat and depression.**

<table>
<thead>
<tr>
<th>Study [Ref]</th>
<th>Sample</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kahl et al. 2005 [26]</td>
<td>18 women: MDD+BPD 18 women: MDD-no-BPD 12 women: BPD-no-MDD 20 women: healthy controls</td>
<td>Increased visceral fat (quantified by magnetic resonance tomography) in MDD+BPD (p=0.023) and MDD-no-BPD (p=0.048)</td>
</tr>
<tr>
<td>Lee et al. 2005 [27]</td>
<td>Overweight females n=101</td>
<td>Zung Depression scale showed a positive association with visceral adipose tissue but not subcutaneous adipose tissue (measured using computed tomography)</td>
</tr>
<tr>
<td>Papakostas et al. 2005 [28]</td>
<td>MDD outpatients in fluoxetine trial n=369</td>
<td>At baseline 51.4% were overweight (BMI ≥25; 47.2% of women, 56.5% of men); 20.0% (25.1% of women, 14.1% of men) were obese (BMI ≥30)</td>
</tr>
<tr>
<td>McIntyre et al. 2006 [29]</td>
<td>Community survey n=36 984; age ≥15 years</td>
<td>A history MDD was more likely if BMI &gt;30 (19% vs. 15%). Lifetime MDD was more likely in obese women (OR 1.22) but not men</td>
</tr>
<tr>
<td>Ohayon 2006 [30]</td>
<td>Community interview n=6694, age ≥18 years</td>
<td>5.4% met criteria for MDD; obesity (BMI &gt;30) correlated with MDD (bivariate OR 1.7)</td>
</tr>
<tr>
<td>Simon et al. 2006 [31]</td>
<td>National Comorbidity Survey Replication; n=9125</td>
<td>Lifetime prevalence of MDD was 18.6% if BMI ≥30 vs.16.0% of BMI &lt;30 (OR 1.21). ORs for bipolar disorder, anxiety disorder, and substance use disorder were 1.47, 1.28, and 0.78, respectively.</td>
</tr>
<tr>
<td>Kloiber et al. 2007 [32]</td>
<td>MDD inpatients n=408; matched controls n=1029</td>
<td>Significantly higher BMI for MDD patients vs. healthy controls (25.05±4.3 vs. 24.42±4.0; p&lt;0.01)</td>
</tr>
<tr>
<td>Goethe et al. 2007 [19]</td>
<td>MDD inpatients n=912</td>
<td>Prevalence 43.8% (n=328); increased WC associated with age ≥40 years (OR 1.91) and female sex (OR 4.46)</td>
</tr>
</tbody>
</table>

BMI: body mass index; BPD: borderline personality disorder; MDD: major depressive disorder; OR: odds ratio; WC: waist circumference.
Table 3. Summary of studies investigating diabetes and depression from 2003 to present day.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Sample</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egede et al. 2003 [34]</td>
<td>176 with DM; 1873 without DM</td>
<td>CIDI-SF; MDD prevalence: 9.3% in diabetics vs. 6.1% in non-diabetics</td>
</tr>
<tr>
<td>Finkelstein et al. 2003 [35]</td>
<td>Medicare Claims data aged ≥65 years; n &gt;220,000</td>
<td>Claims diagnosis of MDD Prevalence of MDD: 2.85% of DM patients vs. 1.88% of non-DM patients, OR 1.58</td>
</tr>
<tr>
<td>Lawlor et al. 2003 [36]</td>
<td>4286 women, aged 60–79 years</td>
<td>Three measures of depression: 1) receiving antidepressant treatment, 2) patient-reported history of depression, 3) yes answer to “feeling either moderately or extremely anxious and/or depressed today”. Among non-diabetics, prevalence of depression decreased with increasing insulin resistance (HOMA categorized into quartiles); depression prevalence increased among DM patients</td>
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<tr>
<td>Everson-Rose et al. 2004 [20]</td>
<td>Women (n=2662) aged 42–52 years; non-diabetic at baseline; follow-up over 3 years</td>
<td>Baseline CES-D ≥16. Depressed patients n=606, 22.8% Depressed patients had higher HOMO-IR (p=0.038) controlling for demographics, study site, education, medication. DM more likely to develop over follow-up in women depressed at baseline (OR 1.66)</td>
</tr>
<tr>
<td>Kopf et al. 2004 [37]</td>
<td>78 depressed patients aged 21–87 years; 69% female</td>
<td>MDD (DSM criteria) and HAM-D ≥18 For BMI &lt;25 kg/m² – insulin sensitivity negatively correlated with cortisol For BMI &gt;25 kg/m² – insulin sensitivity positively correlated with BMI For BMI &gt;25 mg/m² – hypercortisolemia negatively correlated with total %LDL cholesterol</td>
</tr>
<tr>
<td>van den Akker et al. 2004 [38]</td>
<td>Retrospective cohort 1334 depressed patients; 66 670 birth year-matched non-depressed controls</td>
<td>Diagnosis of depressive disorder or affective psychosis (ICCHPPC-2) Follow-up ranged from 1 month to 25 years (no significant difference between groups) Overall 6.7% of depressed developed DM vs. 4.7% of non-depressed (HR 1.04, N5). Significant increase in DM in men, aged &lt;50 years (HR 1.78, CI 1.21–2.62)</td>
</tr>
<tr>
<td>Kahl et al. 2005 [26]</td>
<td>18 women: MDD+BPD 18 women: MDD-no-BPD 12 women: BPD-no-MDD 20 women: healthy controls</td>
<td>Increased insulin resistance in MDD+BPD compared with control group (p=0.001) and trend toward increased insulin resistance compared with BPD-no-MDD (p=0.076). Increased FBS in MDD+BPD compared with controls (p=0.048). Trend toward increased FBS in MDD-no-BPD compared with controls (p=0.081)</td>
</tr>
<tr>
<td>Patten et al. 2005 [39]</td>
<td>Canadian Community Health Survey; aged ≥18 years; n=115,071</td>
<td>CIDI-SFMD: endorsing ≥5 symptoms: 12-month prevalence of MDD 7.4% 12-month prevalence among patients with DM 7.7% (adj OR 1.4, Cl 1.2–1.6)</td>
</tr>
<tr>
<td>Timonen et al. 2005 [40]</td>
<td>Cross-sectional cohort Aged 55 years, n=491</td>
<td>Negative correlation (r=-0.15, p=0.004) between BDI-21 scores and insulin sensitivity check index. For those with impaired GTT, median BDI was 6 vs. 5 for those with non-impaired GTT</td>
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<tr>
<td>Heiskanen et al. 2006 [17]</td>
<td>121 depressed patients at baseline cross-sectional design 6 year follow up</td>
<td>SCID-I (72% MDD, 1% bipolar, 27% other depression) At 6-year follow-up 48% had elevated FBS</td>
</tr>
<tr>
<td>Weber-Hamann et al. 2006 [41]</td>
<td>80 non-DM MDD inpatients</td>
<td>DSM and HAM-D ≥18; GTT at baseline and after 35 days of antidepressant treatment. At baseline 6.2% had impaired FBS, 31.2% had IGT, 20% had DM. Post-treatment insulin sensitivity increased only in those patients whose depression remitted (p&lt;0.01)</td>
</tr>
<tr>
<td>Almeida et al. 2007 [42]</td>
<td>Cross-sectional community sample 4204 men, aged 71–89 years</td>
<td>212 depressed patients (5%; GDS ≥7). Depressed patients reported higher incidence of DM (23.1% vs. 13.2%)</td>
</tr>
<tr>
<td>Kno et al. 2007 [43]</td>
<td>102 diagnosed T2DM 55 undiagnosed T2DM 671 impaired FBS 3499 normal FBS</td>
<td>Depression defined as ≥25 on SCL-90 depression subscale and/or use of antidepressants. Depression prevalence significantly greater in diagnosed T2DM (29.7%, OR 1.69), but not in undiagnosed T2DM (20.0%) or impaired FBS (17.5%) compared with normal FBS (19.4%)</td>
</tr>
</tbody>
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Based on American Diabetes Association categorized FBS. BDI: Beck Depression Inventory; BPD: borderline personality disorder; CES-D: Center for Epidemiological Survey-Depression scale; CI: confidence interval; CIDI-SF: Composite International Diagnostic Interview; CIDI-SFMD: Composite International Diagnostic Interview – Short Form for Major Depression; DM: diabetes mellitus; FBS: fasting blood sugar; GDS: Geriatric Depression Score; GTT: Glucose Tolerance Test; HAM-D: Hamilton Rating Scale for Depression – 21-item version; HOMA: Homeostasis Model Assessment; HOMA-IR: Homeostasis Model Assessment–Insulin Resistance; HR: hazard ratio; ICHPPC-2: International Classification of Health Problems in Primary Care; IGT: impaired glucose tolerance; LDL: low-density lipoprotein cholesterol; MDD: major depressive disorder; NS: non-significant; OR: odds ratio; SCL: Symptom Check List.
governed by genetic factors and “hyper-reactivity of the sympathetic nervous system”, rather than by any unidirectional association between this psychiatric disorder and blood pressure [71].

**Antidepressant medication and MetS**

Antidepressant medications, in contrast to antipsychotics, have not been systematically examined as potential risk factors for MetS under its current definition. However, there are a number of studies and case reports that suggest associations between these agents and individual MetS measures. This section summarizes the literature for each class of antidepressant currently available in the US.

**Monoamine oxidase inhibitors**

Monoamine oxidase inhibitors (MAOIs) have been available in the US since 1957 [72]. Phenelzine, tranylcypromine, and isocarboxazid are the three principal drugs in this class; iproniazid was briefly available but was withdrawn from the US market due to hepatotoxicity [72]. These agents are believed to enhance serotonin, norepinephrine, and dopamine. As a class, the MAOIs are associated with weight gain [73], but there are more reports implicating phenelzine than either tranylcypromine or isocarboxazid [73–77].

Weight gain during phenelzine treatment has been reported as ≥15 lbs (6.8kg) in several cases, and 44 lbs (19.9kg) in one patient [73]. The mechanism of MAOI-induced weight gain is not clear, but may be related to stimulation of carbohydrate craving or to reduced blood glucose. A decrease in glucose level has been reported in both laboratory and clinical studies [78–82], and in one report hypoglycemia occurred 3–4 weeks after initiation of treatment [83]. MAOIs also appear to increase sensitivity to or production of insulin [84–86], although the clinical significance of this finding is unclear.

To the current authors’ knowledge, there are no published data to suggest that MAOIs affect either cholesterol or triglycerides. Orthostatic hypotension is common and hypertensive crisis can occur [79], but MAOIs are not associated with sustained elevation of blood pressure. Thus, there is little to suggest an association between MetS and MAOIs, although for some patients obesity could be a complication of treatment with this class of antidepressants.

**Tricyclic antidepressants**

The tricyclic antidepressants (TCAs) are a large group of medications that have variable effects on the reuptake of both norepinephrine and serotonin. They are known antagonists of histamine-1, muscarinic-1, and alpha-1 receptors. Weight gain is an anticipated adverse effect of TCA treatment [87]. In general, the tertiary TCAs (amitriptyline and imipramine) appear to have a greater propensity for this adverse effect than the secondary amines (nortriptyline and desipramine) due to their higher relative affinities for the histamine-1 receptor. In a study of 52 patients treated with imipramine 200–250 mg/day for 16 weeks, Fernstrom et al. found that 6% of patients gained ≥15 lbs (6.8kg), 9% gained 11–15 lbs (5–6.8kg), and 19% gained 6–10 lbs (2.7–4.5kg); however, 60% of patients did not gain weight and 6% lost 6–10 lbs (2.7–4.5kg) [88]. In an inpatient study, those treated with amitriptyline gained more weight on average after 8 weeks compared with those in the desipramine or fluoxetine group [89].

Another anticipated adverse effect of the TCAs is orthostatic hypotension, often with reflux tachycardia. However, there are also case reports of hypertension implicating imipramine, clomipramine, and amitriptyline, although the number of cases is small (n=1, 3, and 1, respectively) [90–94]. In each of these cases, medication discontinuation resulted in a return to normal blood pressure. Elevated blood pressure has also been reported with TCA use in patients with panic disorder [93] and bulimia [94]. Louie et al. found that 5% of 114 patients with panic disorder who were taking a TCA developed hypertension [93]. Three of these patients had a pre-existing diagnosis of hypertension treated with an anti-hypertensive, and three had a co-diagnosis of MDD. Walsh et al. reported that 74 patients with bulimia nervosa treated with desipramine for 6 weeks experienced an average increase in reclining systolic and diastolic blood pressure of 10 mmHg [94]. Nonetheless, elevations in blood pressure appear infrequent.

An increase in total serum cholesterol levels has been reported for both imipramine and doxepin [95,96]. Yergani et al. retrospectively examined 24 patients treated with imipramine for panic disorder; total cholesterol levels increased from an average of 202 mg/dL to an average of 215 mg/dL 12 weeks later (p<0.05). Roessner described a 32-year-old white female with a total cholesterol level ranging 201–221 mg/dL during 20 weeks of venlafaxine treatment [96]; after a switch to doxepin, her total cholesterol levels increased to 320 mg/dL in the 25th week of treatment. Yergani et al. [97] and Kopf et al. [98] have suggested that treatment with imipramine and amitriptyline may each be associated with small reductions in HDL cholesterol, while it has also been noted that amitriptyline and nortriptyline may be associated with increases in triglyceride levels [98,99]. Several reports also indicate that glucose dysregulation may be a relatively frequent finding in patients treated with TCAs, most commonly imipramine and amitriptyline [100–104].

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**The Metabolic Syndrome and Depression: A Review**
Selective serotonin reuptake inhibitors
The selective serotonin reuptake inhibitors (SSRIs) are a chemically diverse group of antidepressants with a common pharmacology. Based on their purported mechanism of action, SSRIs would not be expected to be strongly associated with MetS. In a controlled trial, only 1.8% of SSRI-treated subjects had a weight gain of ≥7% at 6–8 weeks; however, at 16–46 weeks 17.9% of SSRI-treated subjects had experienced a weight gain of the same magnitude [105]. In another study, patients treated with fluoxetine, sertraline, or paroxetine were followed for 32 weeks to identify the extent and direction of weight change [106]. On average, both sertraline- and paroxetine-treated patients gained weight (1% and 3.6% of body weight, respectively), while fluoxetine-treated patients lost weight (0.2% of body weight). These findings were observed in 4.2% of sertraline-, 6.8% of fluoxetine-, and 25.5% of paroxetine-treated patients. In addition, significantly more paroxetine-treated patients gained ≥7% of baseline body weight at 32 weeks compared with either sertraline- or fluoxetine-treated patients.

Citing data from the Hordaland Health Study, Raeder et al. found a significant association between SSRI treatment and both central obesity and hypercholesterolemia [107]; a trend was also noted for SSRI treatment and diabetes. Paroxetine and citalopram were the two most commonly used SSRIs, accounting for 41% and 31% of the prescribed agents, respectively. The unadjusted prevalence rates of central obesity and hypercholesterolemia for all SSRI-treated subjects were 24.8% and 32.6%, respectively; 11.4% of SSRI-treated patients had both findings. The investigators concluded that there is an association between paroxetine treatment and central obesity, and that treatment with SSRIs other than citalopram or paroxetine is associated with both central obesity and hypercholesterolemia. Thus, SSRIs appear to increase the risk of weight gain, although this side effect may only be evident after extended treatment.

There are only a few reports that address the effects of SSRIs on cholesterol or triglycerides [98,108,109]. Small increases in low density lipoprotein (LDL) cholesterol concentrations have been reported for both paroxetine and sertraline. Lara et al. found that 18 healthy males exposed to paroxetine 20 mg/day for 8 weeks had an average increase of 9 mg/dL in LDL cholesterol but no change in HDL cholesterol or triglycerides [108]. Bailey and Le Medéllo also found that in panic disorder patients, SSRI treatment was associated with a 31 mg/dL increase in low density lipoprotein (LDL) cholesterol, and a 61 mg/dL increase in total cholesterol, but no change in triglycerides [109]. Conversely, Kopf et al. reported that paroxetine 40 mg/day given to depressed patients for 7 weeks was not associated with any change in cholesterol or triglycerides [98], and fluvoxamine treatment in patients with obsessive–compulsive disorder has been associated with a reduction in total cholesterol levels [110].

SSRI effects on blood glucose concentrations appear to be minor. In a controlled trial, Ghaeli et al. found that FBS decreased slightly (mean 8.7 mg/dL) during treatment with fluoxetine 20–40 mg/day for 8 weeks [103]. In another small trial, S-citalopram treatment in a sample of depressed patients with comorbid diabetes was associated with a non-significant reduction in blood glucose and glycosolated hemoglobin (HbA1c) over 16 weeks [111]. After 6 months paroxetine 20 mg/day was associated with no changes in glycemic control in depressed patients with diabetes [112]. In two case reports sertraline was found to be associated with both hypoglycemia and hyperglycemia [113,114].

Other antidepressants
Bupropion
Bupropion was approved by the US Food and Drug Administration in the 1980s and is the only antidepressant that has norepinephrine and dopamine reuptake inhibition properties. In early studies, bupropion was believed to be a suitable choice for patients with MDD and comorbid heart disease because it did not adversely affect supine or standing blood pressures, nor did it slow cardiac conduction [115]. In patients with co-existing CVD, bupropion treatment has not been associated with any changes in heart rate or blood pressure compared with baseline values. Additional research, however, has indicated that bupropion is associated with small elevations in blood pressure. Kiev et al. found that supine diastolic blood pressures increased an average of 7.5 mmHg at the end of 28 days of treatment on bupropion doses of 225–450 mg/day [116]. Wilens et al. reported similar effects in adult patients treated for attention deficit hyperactivity disorder [117]. Bupropion treatment was associated with a mean increase in systolic blood pressure of 5.9 mmHg. This finding is comparable to the 5.4 mmHg increase in blood pressure associated with amphetamine treatment.

Improvements in glycemic control have been reported in depressed patients with type 2 diabetes treated with bupropion [118]. During 24 weeks of treatment with bupropion, patients’ HbA1c levels were reduced by an average of 0.7%. We are aware of no reports that address the issue of serum lipid changes associated with bupropion treatment for MDD, but Gadde et al. reported that eight patients who had been receiving olanzapine 10 mg/day for an average of 2 years had lipid and weight improvements after receiving bupropion 300 mg/day for 24 weeks [119]. In these eight patients, both WC and total cholesterol levels improved significantly from baseline. Change in WC was
from 109.1±4.6 cm at baseline to 103.7±5.0 cm (p=0.028) and total cholesterol values changed from 218.0±3.9 mg/dL to 188.1±8.2 mg/dL. All other lipid values, including LDL, HDL, and triglycerides, improved to a small extent over this time period, but none of the changes were statistically significant (p=0.100, p=0.219, and p=0.602, respectively). These data support the conclusion that bupropion is associated with at least some weight loss over time [120].

**Duloxetine**

Duloxetine is a serotonin–norepinephrine reuptake inhibitor (SNRI) that is in some ways similar to venlafaxine. Blood pressure increases with duloxetine appear to be minor [121], based on two pooled analyses [122,123]. The effects of “supratherapeutic” doses of duloxetine have also been studied. Derby et al. reported that in 117 healthy women given doses ranging from 60 mg twice daily to 200 mg twice daily, duloxetine treatment was associated with maximum increases in blood pressure of 12 mmHg (systolic) and 7 mmHg (diastolic) [124]. The effects of duloxetine on FBS and lipid levels appear to be minor [125]. In an analysis of 1024 adult patients with diabetic peripheral neuropathy, duloxetine treatment was associated with small average changes in glucose and HbA1c levels [125]. Plasma glucose levels increased an average of approximately 12 mg/dL over the course of 52 weeks; HbA1c levels increased an average of 0.52%. Average effects on serum lipids were also minor. Levels of triglycerides, total cholesterol, and LDL cholesterol increased by 0.8–4.3 mg/dL over 52 weeks. Duloxetine is associated with a small reduction in weight during the initial weeks of treatment; as treatment progresses, weight increases to slightly above that at baseline [124,126].

**Mirtazapine**

Mirtazapine is a pre-synaptic alpha 2 receptor antagonist with antihistamine effects that has been associated with weight gain and with increases in both cholesterol and triglycerides [127,128]. Product labeling, based on early clinical trials, states that weight gain and increases in non-fasting serum cholesterol and triglycerides occur in 8%, 15%, and 6% of subjects, respectively [129]. Subsequent study results have been consistent. Laimer et al. reported a significant change from baseline (mean 7 kg; p=0.01) in seven depressed women treated with mirtazapine for 6 weeks [130]. Total, LDL, and HDL cholesterol, and triglyceride levels did not change significantly. The results of Nicholas et al. were similar in a sample of 28 healthy subjects given mirtazapine for 4 weeks [131]. Weight gain was not dramatic (mean 1.64 kg, 2.5% of mean body weight), but was statistically significant when controlling for gender (p=0.0002). Mean increase in total cholesterol level was also modest but statistically significant (7 mg/dL; p=0.016); LDL and HDL cholesterol and triglyceride levels did not change.

**Venlafaxine**

Venlafaxine is a SNRI with a relatively greater affinity for the serotonin pump. The primary concern with venlafaxine is elevated blood pressure. This drug appears to have little effect on weight gain and serum glucose, although there are few published studies investigating this. Venlafaxine-treated patients may initially lose a small amount of weight [132], a finding reinforced by a pooled analysis comparing venlafaxine with duloxetine [133]. Venlafaxine-treated subjects (n=337) had a mean weight loss of 0.34 kg over 12 weeks. In a review of the effects of antidepressants on glucose homeostasis, McIntyre et al. concluded that SNRIs do not disrupt glucose homeostatis dynamics [134]. There are no known data on the effects of venlafaxine on cholesterol or triglycerides.

**Atypical antipsychotics**

The atypical antipsychotics are best known for their use in the treatment of schizophrenia, but there is accumulating evidence that they may also play an important role in the treatment of MDD. The typical antipsychotics (in particular the low-potency agents) were the first psychotropics to be associated with the adverse effects of weight gain, dyslipidemia, and hyperglycemia, but it is now known that the atypical antipsychotics, especially olanzapine and clozapine, confer a greater risk of these events (for an example, see Newcomer [135] and the Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes [14]). Quetiapine and risperidone are associated with a moderate risk of these adverse effects, and ziprasidone and aripiprazole are thought to be associated with a relatively low risk [135]. MetS risk has not been established for paliperidone, the primary metabolite of risperidone, but it is likely that its side effect profile is similar to that of risperidone.

**Clinical implications and recommendations**

Studies to date have identified multiple associations between depression and various metabolic measures, but there are few data to support definitive conclusions about how these measures may be related. One of the mechanisms proposed suggests a link between factors that may contribute to both mental illness and to altered metabolic function. Stress and the body’s response to stress have been associated with psychiatric illness since the work of Walter Cannon [136]. Broadly speaking, any emotional or physical trauma, perhaps especially if sustained, could produce physiological changes...
JOHN W GOETHE, BONNIE L SZAREK, AND CHARLES F CALEY

linked to MetS (e.g. elevated cortisol levels). In a recent review Rääkkönen et al. suggested that depressive symptoms, overall stress, and certain intense feelings, when experienced frequently, contribute to the development of MetS [18]. Such an association may be particularly strong with relation to body fat criterion [25,49,137]. Whatever the mechanism, both the causes and effects of alterations in metabolic functions probably vary widely due to factors such as genetic differences, the health status of an individual, and the availability and effectiveness of treatment interventions.

Clinically, the presence of even one of the components of MetS is of concern [138]. MetS criteria appear to be interrelated, and an intervention when only one is present may prevent progression to the full syndrome, decreasing the patient’s health risks [4]. For psychiatric patients, early detection of a metabolic “signal” may be an opportunity for a change in pharmacotherapy as well as for medical intervention.

There is a clear need for routine monitoring of depressed patients to ensure early detection of any of the MetS criteria. Avoiding metabolic complications should be part of an early intervention strategy; the English proverb “an ounce of prevention is worth a pound of cure” may apply here in a literal sense. In the future, genotyping may allow identification of patients who are susceptible to MetS [139]; however, for the present, practitioners should stress the importance of diet and exercise and carefully assess the risk of MetS when selecting among the available pharmacotherapeutic options. Guidelines for monitoring patients at risk of MetS have been widely circulated (for example 4,14,140), and depression should be added to the list of conditions for which ongoing monitoring is recommended. The data cited in this manuscript suggest that patients with depression, as well as those with schizophrenia or exposed to antipsychotics, are at very high risk of MetS.

Among the causes of variability in the reported prevalence of MetS are differences in the gender and ethnic composition of the patient samples being assessed. Hypertriglyceridemia, for example, is more common in white and Mexican Americans than in African Americans [141]. Hypertension occurs more frequently in African Americans, and diabetes more frequently among Latinos [142]. White people are at a greater risk of developing diabetes compared with several other ethnic groups [143–145], and since high blood pressure is twice as frequent in individuals with diabetes, many white people will have both conditions [146]. Similarly, in Latinos there is a high prevalence of both obesity and diabetes [147], and they are more likely than white and black individuals to have at least two criteria of MetS [148]. How these variables play out in psychiatric populations is not fully understood. It is likely that there are genetic factors that contribute to these ethnic patterns, as well as lifestyle variables [142].

Some but not all studies of MetS and depression have found a difference in prevalence by gender. In the Kinder et al. community study, MetS and female sex were associated with depression, and only individuals receiving treatment for long-standing depression were included – factors that may have reduced the likelihood of detecting a gender difference. A study of depressed inpatients (n=52) found a gender difference for the ATP III WC criterion (24.5% of men vs. 8.1% of women) [19], but not for the prevalence of the syndrome. There was a gender difference in MetS prevalence (5.16% for females vs. 36.0% for males) in outpatients with schizophrenia in CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) [22].

Community [21], as well as clinical [16,17], samples show that females have a greater total number of MetS measures and that there are gender differences in the prevalence of some of these measures. For example, using 1999–2000 community data (NHANES; National Health and Nutrition Examination Surveys) and the ATP III criteria, Ford et al. found that 51.9% of females compared with 36.0% of males met the WC criterion [21]; by contrast, a higher proportion of men met the FBS criterion (≥100 mg/L or using medication for diabetes mellitus, 37.7% vs. 23.8%) [21]. The two lipid measures and the blood pressure criterion were similar for men and women, ranging in prevalence from 29.9% to 43.4% [21].

The majority of the literature regarding the health risks associated with MetS refers only to cardiovascular concerns, but there is a growing body of evidence that suggests an association with cognitive impairment and dementia. For example, the presence of MetS [149], elevated LDL [150], and the triad of obesity, total cholesterol, and elevated systolic pressure [151] in mid-life have been found to be associated with the later development of dementia. Diabetes patients with MetS have been found to more frequently have impaired cognition compared with those without MetS [152], and in a similar study the MetS group contained significantly more patients with a diagnosis of dementia [153]. Among geriatric patients without dementia, those with MetS more frequently develop Alzheimer’s disease [154]. Thus, early intervention in MetS may not only reduce premature mortality and morbidity associated with CVD, but may also prevent or delay the onset of cognitive decline.

While research efforts will continue to focus on the many unanswered questions about MetS, the chief focus for practitioners is to ensure that depressed patients have
routine assessments for MetS as well as prompt and appropriate intervention when any MetS criterion is identified. Revisions to current guidelines will address the need for consensus, but should also attend to other issues important in clinical care. What is known about individual variability in metabolic measures should be reflected, eventually creating population-specific MetS criteria; alternative measures could be substituted based on age, gender, ethnicity, psychiatric diagnosis, or other features. Guidelines should quantify differences in the change in risk associated with improvement or progression of a given problem/MetS criterion, such as whether an individual taking antihypertensive medication and currently normotensive is still at increased risk? Are there incremental increases in risk in severe versus mild obesity? Finally, weighted criteria may be needed to allow more specific determination of risk in any given patient.

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References
THE METABOLIC SYNDROME AND DEPRESSION: A REVIEW

Late-life depression is not uncommon, occurring in approximately 2% of all community-dwelling elderly people [1,2]. In patients admitted to acute care hospitals, the prevalence increases to 10–12%, while among nursing home residents, 12–14% meet the criteria for a major depressive disorder (MDD) [3]. Moreover, in the US, it has been found that the presence of depressive symptoms is much higher in the elderly, with studies showing prevalence rates between 30% and 45% [1,4]. In this review, the term “depression” is used to indicate a MDD.

Depression is a serious illness that increases the morbidity and mortality rate in the elderly. Older patients with depression have a 1.5–3-fold increased morbidity rate when compared with non-depressed elderly and a lifetime suicide risk of approximately 15% [1]. Almost 10% of depressed elderly individuals die annually from suicide [1]. Given that depression has broad-reaching clinical significance, it is imperative for the primary care and psychiatric communities to appreciate the unique presentation, diagnosis, and treatment of depression in geriatric patients compared with the general population. Table 1 describes the DSM-IV-TR criteria for diagnosing depression [5].

Late-life depression is described as depression arising in adults aged >65 years who do not have a previous history of mood disorder [3]. Table 2 lists the salient features of late-life depression.

Dementia and depression can easily mimic each other and care must be taken to ensure a proper diagnosis, as both the treatment and prognosis differ greatly between these two conditions [10]. Dementia of depression (previously called pseudodementia) refers to the reversible cognitive impairment seen in the setting of a depressive episode, which improves with the treatment of that episode [1,3]. Conversely, depression can be an early presenting symptom of dementia. It remains unclear whether depression is a prodrome for the onset of dementia, a risk factor for dementia, or an independent event [6]. Features that distinguish depression-associated dementia from depression are listed in Table 3.

Depression results in far-reaching health and social consequences and the risk factors for the development of late-life depression and its consequences are listed in Tables 4 and 5.

A complex relationship exists between mood disturbances, cognitive function, and somatic complaints; therefore, an elderly patient presenting to the primary care clinic with multiple unexplained medical complaints and/or cognitive decline should be screened for depression. During the work-up for depression in late life, a full medical and psychiatric assessment should be completed to rule out the presence of electrolyte and endocrine abnormalities, neurological disorders, inappropriate medication use, substance abuse, and comorbid psychiatric disorders. Cognitive evaluation should include a
Folstein Mini Mental State Examination (MMSE), a clock drawing test, and Executive Interview (EXIT); a neuropsychological evaluation should be performed if the presence of cognitive deficits is uncertain from the above mentioned screening tools [12–14]. If depression is suspected, prompt treatment often alleviates the somatic symptoms and/or cognitive deficits.

As there is a high prevalence of depression and dementia in the elderly, it is recommended that routine screening for late-life depression and cognitive deficits be completed during an annual medical review in order to ensure correct and timely diagnosis of these two important disorders. Screening tools can often be useful in the assessment of patients with depression. These tools not only help detect depression, but also to rate its severity and assess the response to treatment. In this review, we discuss various screening tools available for the diagnosis of late-life depression and indicate their place in the algorithm of the treatment for this serious condition.

Screening tools

Screening tools for late-life depression can be divided into four separate groups. The first involves those tools designed specifically for elderly patients with depression; the second includes tools that were not designed specifically for elderly patients, but are commonly used in depression studies in the elderly; the third group involves tools that are designed specifically for the elderly, but not to rate depression alone; while the fourth involves those tools that are not specific to the elderly or for rating depression, but are commonly used in depression studies in the elderly.

Tools specifically designed for elderly patients with depression

Geriatric Depression Scale
The Geriatric Depression Scale (GDS) was developed in 1983 as a tool to specifically measure depression in an older patient population. It was designed to be a simple-to-administer test that would not require the skill of a trained interviewer and could differentiate depressive symptoms from general traits present in an elderly population [15]. Somatic symptoms were not addressed in order to avoid overlap with medical conditions frequently present in the elderly, and symptoms related to psychosis were also excluded. The original test consisted of 100 “yes” or “no” questions, but was reduced to a 30-item scale that can be self-administered or given by an interviewer, taking 5–10 minutes to conduct [16]. A sensitivity of 84% and a specificity of 95% have been demonstrated using a cutoff score of 11. If the cutoff is increased to 14, the sensitivity drops to 80% but the specificity increases to 100% [15]. The 30-item scale has been further condensed to a shorter version containing the 15 items from the original GDS that most closely correlated with depressive symptoms [17]. Comparisons between the short and long forms of the GDS using a cutoff score of ≥5 have demonstrated a high correlation (r=0.89) and similar sensitivity rates [18]. However, in patients who have more severe dementia, the GDS may not be an adequate screening tool [19,20], and some authors have found decreased utility in cognitively intact patients who are considered “old-old” (aged >75 years) [21]. Another disadvantage of the GDS is that it does not address suicidal behaviors.

Cornell Scale for Depression in Dementia
The Cornell Scale for Depression in Dementia (CSDD) was designed to assess depression in patients with dementia [22]. This test is administered by a clinician during which time 20 min are spent with the caregiver and 10 min with the patient[16]. Factors assessed by the CSDD fall into four symptom clusters [23]:

- General depression.
- Biological rhythm disturbances.
- Agitation/psychosis.
- Negative symptoms.
There are 19 items included in the CSDD, and the symptoms are scored as “absent” (0), “mild or intermittent” (1), or “severe” (2). A notation is made by the clinician if the score cannot be evaluated for a particular item. Scores are calculated out of a possible total score of 38, with higher scores indicating a greater degree of depression. A score ≥ 8 generally suggests significant depressive symptoms, although 6 was found to be the optimal cutoff score in a recent Danish study [24]. The CSDD has shown validity and reliability in both demented and non-demented patients, and in both hospital and outpatient settings [25,26].

Tools not specifically designed for, but commonly used in, depression studies in the elderly

*Brief Assessment Schedule Depression Cards*

The Brief Assessment Schedule Depression Cards (BASDEC) is based on the depression scale of the Brief Assessment Schedule, which was developed by Macdonald et al. in 1982.
It consists of 19 individual items including statements such as “I’m not happy at all” and “I seem to have lost my appetite” [27]. The BASDEC evolved from the Brief Assessment Schedule as a means to prevent such statements being overheard in residential facilities or geriatric wards. The statements were transcribed onto 19 individual cards that the patient could then sort into either a “true,” “false,” or “I don’t know” pile [28]. Cards in the “true” pile have a value of 1 point, those in the “I don’t know pile” a value of 0.5, and cards in the “false” pile receive no score. There are exceptions to this scoring system, however, and the statements “I’ve given up hope” and “I’ve seriously considered suicide” have a value of 2 points if rated “true” and of 1 point if rated “I don’t know” [16]. A patient with a total score ≥7 points is considered likely to be suffering from a depressive disorder. The BASDEC has been found to be a valid and sensitive screening tool for depression in medically ill patients in both community and hospital settings [28–30].

**Center for Epidemiological Studies – Depression Scale**

The Center for Epidemiological Studies – Depression Scale (CES–D) was originally developed for a large population study and was designed to categorize depressive symptoms [31]. It was then modified into a 20-item, self-administered assessment that takes approximately 5 min to complete. Symptoms are categorized into four main areas: depressed affect, positive affect, somatic/vegetative signs, and interpersonal distress. Patients are asked to consider their depressive symptoms over the past week and then rank the frequency of these feelings from “rarely” (<1 day) to “most of the time” (5–7 days). The scoring ranges from 0–60 and a systematic review has shown that, in cutoffs ranges of 9–21, the sensitivities and specificities range from 75–93% and 73–87%, respectively [32]. Although this test was developed for the general population, it has been found to have a similar performance in mildly demented and cognitively intact patients; however, it is probably not effective in moderately or severely demented patients [33].

**Hamilton Rating Scale for Depression**

The Hamilton Rating Scale for Depression (HAM-D) was originally designed as a means to assess treatment outcomes rather than as a screening or diagnostic tool for depression [34]. It is administered in a semi-structured format by a trained interviewer and generally takes 20–30 min. The HAM-D is a 21-item scale with 11 items scored 0–4 (absent, slight/doubtful, mild, moderate, severe), and 10 items that can not be expressed quantitatively scored 0–2 (absent, slight/doubtful, clearly present) [16]. Although the original version had 21 items, a 17-item version is more commonly used – the last four items, which do not measure the intensity of depression, are omitted. Generally, a cutoff score of 10 or 11 is viewed as appropriate for a diagnosis of depression. The HAM-D is a widely used observer scale for the evaluation of depression, but has not been well validated in the geriatric population, particularly in those patients with cognitive impairments [35]. Some of the limitations noted for the HAM-D have included the prominence of behavioral and somatic symptoms with less emphasis on self-reported feelings of distress, an overly broad timeframe for which the questions are directed, and poor item reliability [36]. Attempts to address some of these shortcomings have included the use of a modified Structured Interview Guide for the HAM-D (the SIGH-D), which demonstrated improved item reliability and decreased variability in ratings [37].

**Montgomery–Asberg Depression Rating Scale**

The Montgomery–Asberg Depression Rating Scale (MADRS) was originally developed from components of the larger Comprehensive Psychopathological Rating Scale and was designed to measure changes in depression symptoms during treatment [38]. It is an observer-rated scale given by a trained interviewer and takes 20 min to administer.

The MADRS is a well validated rating tool in psychiatry. There are 10 variables including apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, difficulty concentrating, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts, with each variable having six possible ratings [16]. Snaith et al. suggested the following cutoffs [40]:

- 0–6: absence of depression.
- 7–19: mild depression.
- 20–34: moderate depression.
- ≥35: severe depression.

As there is little emphasis on addressing somatic symptoms, the MADRS may be a useful means of assessing depression in a geriatric population or in those patients with chronic illness.

**Zung Self-Rating Depression Scale**

The Zung Self-Rating Depression Scale (SDS) is a self-rating scale that takes approximately 3–7 min to complete. It is commonly used in epidemiological studies and other research, both in geriatric and general patient populations. It has 20 items, and graded responses such as “a little of the time”, “some of the time”, “a good part of the time”, and “most of the time”, are used to assess levels of depression. This graded scale can present difficulty for some elderly patients, and assistance may be required from caregivers or
the examiner. The mean score in older patients is also higher than in younger subjects, which, if using a cutoff of 40 for depression, results in a false-positive rate of 44% [39]. If a cutoff of 60 is used, investigators have found sensitivities of 58–76% and specificities of 82–86% [41,42].

Tools specifically designed for the elderly, but not to rate depression alone

Geriatric Mental State Schedule

The Geriatric Mental State Schedule (GMSS) is a comprehensive assessment scale of psychopathology in elderly patients [43]. It consists of a semi-structured interview given by a trained clinician and generally takes 40–45 min to administer [16]. Although an assessment of global mental health, it is also useful in evaluating depression in geriatric patients in both inpatient and community settings. The GMSS is used with a companion computer program, the Automated Geriatric Examination for Computer Assisted Taxonomy (AGECAT), to provide a diagnosis based on a validated and reliable algorithm [44]. The AGECAT system assesses eight syndrome clusters (organicity, schizophrenia, mania, depression, hypochondriasis, phobias, obsessions, and anxiety neurosis) with a corresponding diagnostic confidence interval (0=no symptoms, 5=very severely affected) to represent the degree of severity in each syndrome cluster. A level of ≥3 represents a significant degree of impairment and would warrant professional evaluation [44]. The GMSS has been translated into many languages, has been widely validated and has high inter-rater reliability, and is seen as a gold standard in many clinical trials in Alzheimer’s disease [47,48].

Brief Psychiatric Rating Scale

The Brief Psychiatric Rating Scale (BPRS) is administered by a trained interviewer and takes 15–30 min to complete. It is an 18-item scale that evaluates a variety of psychiatric symptoms and was designed to assess a patient’s global state. It is rated from 1–7, with higher scores indicating greater severity of depression. Some items are rated based on the interviewer’s observation of the patient (mannersisms, tension, posturing, emotional withdrawal), while other items (anxiety, feelings of guilt, depressed mood) require self-report by the patient [49]. This, like the CGI-C, is frequently used to evaluate change in a patient’s symptoms of depression.

General Health Questionnaire

The General Health Questionnaire (GHQ) was developed in the 1970s as a self-administered instrument to screen for non-psychotic psychiatric disorders [50]. The GHQ is available in 12-, 28-, and 60-question versions, with the time required to complete the test dependent on the version used. It is often utilized in community and non-psychiatric settings. The respondent is asked whether he or she has recently experienced a specific psychiatric symptom, and each item is then rated on a four (0–3) point scale that ranges from “not at all/much less than usual” to “much more than usual.” In addition to being administered in community settings, it is often used as a screening tool in research. The sensitivity and specificity of the GHQ-12 in distinguishing depressive cases from non-depressive cases has been reported as 89% and 80%, respectively [49].

Summary

Although it is not an objective tool, the GDS is the most commonly used screening tool for evaluating late-life depression in primary care clinics and day-treatment programs [39]. It is available in several languages and has been found to be a reliable and valid instrument in large epidemiological studies. However, its validity in patients with moderate to severe cognitive impairment (MMSE <15) is limited [39].

For patients with depression and dementia, the most specific tool available for the screening of depression is the Cornell Scale for Depression in Dementia (CSDD) [39]. However, it has greater accuracy in patients with mild or moderate dementia than in those with severe dementia. Its use is also limited by the need for a trained rater, caregiver input, and the time taken for completion [39].

Screening tools such as the HAM-D, MADRS, and SDS are frequently used in geriatric psychiatry clinics and in research studies with geriatric patients in order to detect depression and to assess response to treatment, despite not
being specific to this subject group. HAM-D is the most commonly used observer-rated scale in late-life depression [39]. Nonetheless, its use is limited by the emphasis on behavioral and somatic symptoms and by the lack of report on feelings of distress, along with the use of associated combinations of frequency and intensity of these symptoms while scoring [39]. Two small studies comparing the GDS and HAM-D have indicated that the GDS is a more sensitive instrument in detecting depressive symptoms in the elderly [39]. In this patient population, the accuracy of the MADRS is limited by the lack of assessment of somatic symptoms, and the applicability of the SDS is limited by its dependence on graded responses, lack of assessment of somatic symptoms, and high false-positive rates [39].

Other scales used in late-life depression include the GMSS, CGI, GHQ, and the BPRS [50]. The GMSS assesses psychopathology including organicity, schizophrenia, mania, depression, hypochondriasis, phobias, obsessions, and anxiety neurosis in elderly patients, whereas the GHQ and CGI assess general mental health and the global level of functioning. The BPRS is commonly employed to detect and rate the severity of psychopathology in an elderly patient with psychotic depression [50]. A brief description of all the tools used in rating late-life depression is provided in Table 6, and an algorithm for using these tools is shown in Figure 1.

### Conclusion
Depression is common in late-life and frequently associated with complications that cause immense suffering to the patient and their families. A number of tools are currently available for the screening of this condition in the elderly. Some, such as the GDS, have been developed specifically for the detection of depression in the elderly. Others, for example the HAM-D, MADRS, and SDS, although not expressly developed for the detection of depression in the elderly, are useful screening tools for depression in this patient population. Psychotic symptoms often complicate the presentation of depression in the older patient and tools like the BPRS can help to detect psychotic symptoms in the depressed elderly. Early detection of depression and its co-morbidities, and their prompt treatment, will help reduce the morbidity and mortality due to this condition, and help alleviate the suffering of all those concerned.

### Disclosures
The authors have no relevant financial interests to disclose.

### References
Figure 1. Algorithm for evaluating late-life depression.

1. Assess for depressive symptoms, cognitive impairment, and general health.
2. Rule out medical and neurological causes for symptoms.
3. Use GDS, MMSE, and GHQ.
4. Presence of depressive symptoms and/or cognitive impairment.
5. Refer to specialty geriatric psychiatry clinic.
6. Depressed patient with cognitive impairment.
7. Use CSDD and MMSE, EXIT, Clock drawing, and CGI-C.
8. Psychotic symptoms.
   a. Use BPRS or GMSS.
   b. Is patient suicidal/homicidal or is self-neglect suspected?
      i. Yes: Hospitalize.
      ii. No: Follow-up patients in the out-patient clinic at 2–4 week intervals.
10. Use MADRS or HAM-D or SDS and CGI-C.

BPRS: Brief Psychiatric Rating Scale; CSDD: Cornell Scale for Depression in Dementia; CGI-C: Clinicians’ Global Impression of Change; EXIT: Executive Interview; GDS: Geriatric Depression Scale; GMSS: Geriatric Mental State Schedule; GHQ: General Health Questionnaire; HAM-D: Hamilton Rating Scale for Depression; MADRS: Montgomery–Asberg Depression Rating Scale; MMSE: Mini Mental State Examination; SDS: Zung Self-Rating Depression Scale.
Exercise and improved mental health

There have been several reports associating exercise with a reduction in depressive symptoms and improvements in other mental health outcomes. Galper et al. examined data from 5451 men and 1277 women enrolled in the Aerobics Center Longitudinal Study, a cohort study that assessed morbidity and mortality rates associated with physical activity and fitness [1]. The Center for Epidemiologic Studies Depression Scale (CES-D), a 20-item self-report scale, was used to quantify depressive symptoms [2], and the General Well-Being Schedule was employed to determine emotional health [3]. In addition, participants completed a comprehensive questionnaire to assess their participation in a wide range of physical activities, and underwent a maximal treadmill exercise test to evaluate physical fitness. Both male and female participants with higher levels of physical activity and physical fitness reported fewer depressive symptoms and greater well-being compared with those with lower levels of activity and fitness.

Similar findings were reported in an investigation involving participants from the BWHS (Black Women’s Health Study), an ongoing research study investigating risk factors for major illnesses in African American women aged 21–69 years. As part of the BWHS, 35 224 participants completed the CES-D and physical activity questionnaires [4]. Vigorous physical activity was associated with a reduced odds ratio (OR) for depressive symptoms in the sample, with the lowest OR observed for women who reported being active in both high school and adulthood (OR 0.76, 95% confidence interval [CI] 0.71–0.82).

Randomized controlled trials of exercise for depression

Exercise has been examined as a treatment for depression, both alone and in conjunction with antidepressant medication. Two recent meta-analyses of exercise research have been conducted [5,6], one of which focused specifically on the elderly [6]. Although both reported that, to date, research in this area is generally favorable towards using exercise to relieve depression, they concluded that rigorously controlled trials are needed to better understand the impact of exercise on this disorder. Recent research has varied significantly with respect to the methods applied to determine diagnoses, the primary outcome measures included, and the exercise interventions used, thus limiting the findings. Despite these limitations, studies performed to date have generally shown exercise to have positive effects on mood in both men and women across a wide age range, irrespective of the setting (from inpatient group exercise sessions to home-based exercise) or mode (aerobic or weight-training). Furthermore, they have demonstrated that patients who continued to exercise following study participation had not relapsed when follow-up was conducted after a period of several months or years. This article will review some of the most salient studies in this area, and identify critical limitations that need to be addressed in future research.

Exercise as a monotherapy

DOSE (the Depression Outcomes Study of Exercise) was one of the first randomized controlled trials to examine the

The Benefits of Exercise for Mood Disorders

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There has been increasing focus in recent years on the role of exercise in mood improvement. Exercise has been associated with a reduced risk of depression and reductions in depressive symptoms, both alone and in combination with antidepressant medication, and there has been extensive investigation into the potential mechanisms by which exercise could exert an antidepressant effect. Moreover, exercise provides additional health and psychosocial benefits, such as improved cardiovascular health and cognitive function. Taken together, these lines of research suggest that exercise is a plausible, effective treatment that is beneficial to individuals suffering from mood disorders. Depression: Mind and Body 2008;3(4):158–65.

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efficacy of exercise as a monotherapy for mild to moderate major depressive disorder (MDD) [7,8]. The investigators used a 2×2 factorial design with a flexibility exercise “placebo” control to examine the effect of different “doses” of exercise on reducing symptoms in men and women aged 20–45 years. The two manipulated exercise factors were total energy expenditure (kcal/kg/week [KKW]) and frequency (days/week). The two doses of total energy expenditure were 7.0 and 17.5 KKW, and the two frequencies were 3 and 5 days/week. Participants were randomized into one of five groups:

- 7.0 KKW over 3 days/week.
- 7.0 KKW over 5 days/week.
- 17.5 KKW over 3 days/week.
- 17.5 KKW over 5 days/week.
- Stretching for 15 min on 3 days/week (flexibility exercise control).

The 17.5 KKW dose translated into 180–210 min of exercise per week (consistent with public health recommendations), and was referred to as the public-health-dose (PHD) cohort. The 7.0 KKW dose translated to approximately 80 min of exercise per week, and was referred to as the low-dose (LD) group. For all conditions, the first 12 weeks of exercise were conducted under supervision, and the remaining 12 weeks of exercise were performed at home or at another facility. The 17-item Hamilton Rating Scale for Depression (HAM-D17) was administered weekly and served as the main outcome measure.

The PHD group showed a 47% reduction in symptoms at 12 weeks compared with reductions of approximately 30% each for the LD and control groups. These represent reductions from a mean baseline HAM-D17 score of 16.0 to scores of 8.5, 11.1, and 11.3 for the three groups, respectively (baseline-adjusted least-squares mean scores). With respect to the main effect of energy expenditure, the PHD group showed significantly greater reductions in adjusted HAM-D17 scores at week 12 compared with the LD and control groups. The difference in remission rates between the PHD group and the control group was significant (p=0.01). Age or gender did not have a significant effect; neither did exercise frequency, suggesting that the amount rather than the frequency of exercise is critical to mood improvement.

More recently, Blumenthal and colleagues reported on the SMILE (Standard Medical Intervention and Long-Term Exercise) study, which examined 202 adults (153 women, 49 men) diagnosed with MDD by structured clinical interview [9]. Participants were randomly assigned to one of four conditions for 16 weeks:

- Supervised group exercise.
- Home-based exercise.
- The selective serotonin reuptake inhibitor (SSRI) sertraline (50–200 mg/day).
- Placebo pill.

The HAM-D was used to quantify depressive symptoms, and the primary outcome measure was the rate of remission (defined as a HAM-D score of <8). Participants randomized to active treatments had higher remission rates than those receiving placebo (supervised exercise 45%, home-based exercise 40%, sertraline 47%, placebo 31%), although this finding did not reach significance (p=0.057). Similarly, all therapy groups had lower HAM-D scores following treatment, but these were not significantly different from the placebo group (p=0.23). Nevertheless, these data indicate that the efficacy of exercise is similar to that of sertraline, a commonly used antidepressant.

Exercise as an augmentation or combination treatment

The vast majority of studies examining exercise as a treatment for depression have investigated exercise in conjunction with concomitant antidepressant medications. Blumenthal et al. compared the effects of group exercise, medication, and group exercise in combination with medication in older adults (aged 50–77 years) with mild to moderate MDD over a 16-week, acute-phase, randomized trial [10]. Their major finding was that group exercise was as efficacious as both medication and combined treatment in reducing symptoms of depression. However, while this study adequately diagnosed depression and measured treatment effects, because the exercise was performed as a group rather than in an individual setting, the question remains as to whether the treatment effects were due to exercise, the social effects of the group, or a combination of the two.

The extension of the Blumenthal study examined the efficacy of exercise in the long-term by conducting a 10-month follow-up of the patients from the earlier acute-phase study [11]. The authors reported a significant overall treatment effect in terms of recovery and relapse rates between the groups (p<0.02). The exercise-alone group had a significantly increased likelihood of recovery (p=0.01) compared with the medication-alone group, and there was a reduced likelihood of relapse in the exercise-alone group (30%) compared with both the medication-alone group (52%) and the combined group (55%). Furthermore, regular aerobic activity was associated with a decreased likelihood of being classified as depressed at follow-up. However, because the follow-up study was naturalistic, many participants changed their treatment regimen following the acute phase but were analyzed as members of
the group they were originally assigned to, which makes interpretation of the results difficult. For example, a person who was in the medication-alone group in the acute phase may have begun exercising after completing this phase, and would therefore technically be undergoing combination therapy when follow-up data were collected. In fact, 48% of the medication-alone group began exercising and 7% of the exercise group began a medication regimen during the 6-month follow-up period. Similarly, not all persons assigned to a particular group continued their therapeutic regimen: 64% of the exercise-alone group continued to exercise and 26% of the medication-alone group continued medication. Several members of the combination group took a monotherapeutic approach after the acute phase, with only 40% of this group continuing to take medication and 66% continuing to exercise. In addition, 16% of the study population as a whole began psychotherapy during follow-up – an approach that was excluded in the acute phase.

Although the variability of many crucial factors was not accounted for in these analyses, such as initiation of new therapy (exercise in the medication-alone group, medication in the exercise-alone group, or psychotherapy in any group), type and dosage of antidepressant used, and the specific variables of continued exercise (e.g. intensity), this study does provide additional support for the use of exercise in the treatment of depression, and suggests that the beneficial effects may be long-lasting.

Martinsen et al. assessed 43 patients hospitalized for depression who were receiving individual psychotherapy and occupational therapy [12], 24 of whom were randomized to a training group in which aerobic exercise was added to existing treatment, and 19 of whom comprised the control group for which there was no exercise added. Although additional therapeutic interventions were not controlled for in the analyses, 14 members of the control group (psychotherapy and occupational therapy alone) and nine members of the training group were taking tricyclic antidepressants while they participated in the study. The authors reported a significantly larger difference in Beck Depression Inventory (BDI) scores between baseline and 9 weeks in the exercise training group compared to the control group (p<0.05).

Similarly, Veale et al. investigated whether the addition of aerobic exercise would benefit participants’ standard treatment for depression [13]. Two related studies were conducted, assessing a combined total of 124 subjects. Enrolled subjects were already receiving a wide variety of treatments for their depression, including antidepressant medications, benzodiazepines, and supportive psychotherapy. In the first study, subjects either continued their usual treatment (control group) or added three supervised aerobic exercise sessions per week (conducted in groups) for 12 weeks. Depressive symptomatology was assessed using the Clinical Interview Schedule (CIS) and the BDI. Mean CIS scores at week 12 were significantly lower in the exercise group (mean 16.80; standard error [SE] 2.06) compared with the control group (mean 26.39; SE 2.50; p<0.005), although reductions in scores were observed for both groups. BDI scores were also reduced in both groups, but no significant differences were found; however, it should be noted that the two groups differed on this measure at baseline (mean and SE scores 22.91 vs. 26.66; SE 1.1 vs. 1.52 for exercise group and control group respectively; p<0.05). In the second study, a low-intensity exercise regimen consisting of stretching and yoga was compared with the aerobic protocol used in the first study. Both types of exercise produced reductions in CIS and BDI scores that were not significantly different between groups at week 12. Again, there were many factors that complicate interpretation of the data, including variable adherence to exercise, group exercise sessions, and baseline group differences in depression severity and antidepressant use.

Dimeo and colleagues conducted a pilot study in which 12 individuals diagnosed with MDD or bipolar I disorder, who were taking antidepressant medications, completed a short-term exercise intervention for 10 days, exercising for 30 min each day [14]. The medications used varied widely and included different types of antidepressants and primary pharmacotherapy with lithium, as well as the use of pharmacological augmenting agents such as neuroleptics and lithium. The HAM-D₂₁ and the Scale for Self-Assessment of Depression were used to quantify depressive symptoms. Significant differences were found between day 1 and day 10 of exercise on both measures, with mean HAM-D₂₁ scores reduced from 19.5±3.3 to 13.1±5.5 (p=0.002) and Scale for Self-Assessment of Depression scores reduced from 23.2±7 to 17.3±8.1 (p=0.006).

More recent studies have examined the effect of the addition of exercise in patients with a partial response to antidepressant medications. One such study sought to examine the efficacy of exercise as an adjunct to treatment with a therapeutic antidepressant medication dosage in older individuals [15]. To be included in the study, participants were required to have been taking their medication for at least 6 weeks with no evidence of a sustained response (as defined by a Geriatric Depression Scale score of ≥10). Eighty-six participants were randomized to attend either group exercise classes (consisting of weight-bearing exercise performed to music) or health education classes (non-exercise control group) twice a week for 10 weeks. In both groups, each session lasted for approximately 45 min. After 10 weeks, 55% (23/42) of the exercise group achieved
a HAM-D$_{17}$ reduction of ≥30%, whereas only 33% (14/43) of the control group achieved such a reduction.

Trivedi et al. conducted an open-label pilot study in depressed individuals (aged 20–45 years) with non-psychotic MDD diagnosed via Structured Clinical Interview [16]. To be eligible for the study, participants had to have received treatment with a SSRI or venlafaxine for at least 6 weeks at a therapeutic dosage, defined as ≥10 mg/day of escitalopram; ≥20 mg/day of paroxetine, citalopram, or fluoxetine; ≥50 mg/day of sertraline; or ≥150 mg/day of venlafaxine. Participants had to report some benefit from antidepressant treatment but still be experiencing residual symptoms, as indicated by a HAM-D$_{17}$ score of ≥14 at study entry. Eligible participants began a 12-week intervention of 16 KKW of aerobic exercise (walking or cycling), which was administered in a combined supervised and home-based protocol. In general, participants reported a moderate level of depressive symptoms at baseline (baseline mean HAM-D$_{17}$ score 17.4). A beneficial effect of the addition of exercise was demonstrated by a reduction of 5.8 points in HAM-D$_{17}$ scores in the intent-to-treat analysis. Improvements in quality of life were also observed. This pilot trial has led to the development of the ongoing TREAD (Treatment with Exercise Augmentation for Depression) study [17], a randomized controlled trial examining SSRI augmentation using a public health recommended dose (16 KKW) or a low dose (4 KKW) of exercise. The investigation is specifically designed to address some of the major existing limitations of exercise studies to date; namely, the use of group exercise, blinded evaluation of outcome measures, and rigorous diagnostic evaluation, and the outcomes are eagerly awaited.

Limitations of exercise research in depression
In general, the studies described have consistently reported a reduction in depressive symptoms as a result of exercise treatment. However, many have methodological flaws, such as the lack of an adequate control group, mixing of treatments, a small sample size, and the absence of clinician-rated assessment of depressive symptoms as an outcome measure or thorough diagnosis of depression. Furthermore, as mentioned above, the exercise interventions used in these trials differ with respect to exercise mode (aerobic versus anaerobic), intensity, and duration, and so it is not possible as yet to adequately define the relationship of these variables with efficacy. Many of the trials examining combination treatment or augmentation of drug therapies with exercise have not adequately controlled for the type, duration, or response to the initial treatment that was combined with exercise. Thus, there remains a need for more rigorously controlled studies in this area.

**Neurobiological support for the use of exercise in mood disorders**
In addition to the available clinical evidence pointing to exercise-induced improvements in mood, several studies on the neural changes observed after exercise support a relationship between exercise and alleviation of depressive symptoms. The alterations seen in many of the neural systems following physical activity resemble the changes observed in response to pharmacological treatment of depression that are believed to be responsible for the alleviation of depressive symptoms. However, most of these studies evaluated neurochemical levels in the brains of animals or peripheral measures believed to represent brain activity, and therefore their direct relevance to exercise as a treatment for depression is not clear. Furthermore, as Dunn and Dishman highlight, these studies assessed a variety of different brain regions, making it difficult to interpret the impact overall [18]. Nonetheless, the overlap between the neural regions and neurochemicals affected by exercise and those involved in depression and antidepressant treatment certainly warrants further investigation. Physical activity has been associated with increased levels of neurotrophic factors, neuromodulators, and neurotransmitters, including brain-derived neurotrophic factor (BDNF) [19–22], norepinephrine [18,23–27], serotonin [18,28–34], and phenylethylamine [35,36].

**Brain-derived neurotrophic factor**
BDNF is one of the most abundant neurotrophins in the brain, and has a wide variety of regulatory functions in neurotransmitter systems. A Ca$^{2+}$/calmodulin-dependent kinase IV-dependent signaling pathway is involved in the regulation of BDNF expression [37], and it has been hypothesized that neuronal stimulation, which elevates intracellular calcium levels, can alter the synthesis of BDNF [38]. When monoaminergic neuronal activation occurs, cyclic adenosine monophosphate- or Ca$^{2+}$-dependent pathways are activated, which can regulate BDNF expression [19,38]. Chronic antidepressant treatment increases BDNF messenger RNA levels, supporting the involvement of monoamines in BDNF expression [21,22,39]. The resultant increases in BDNF levels are associated with an increase in the activity of monoaminergic systems, which are believed to be altered in depression. BDNF has been associated with the promotion of many aspects of serotonin neuronal function, including the growth and regeneration of serotonin neurons [19]. BDNF infusion into the dorsal and median raphe, the origin of the majority of serotonin activity, results in the reversal of the effects of depression-induced behavior in learned helplessness and forced swim test models of depression in rats [20], and this
effect has been likened to that observed in response to antidepressant treatment. Increased BDNF mRNA levels have been observed in the hippocampus and caudal neocortex of rats following voluntary wheel running [29], and Russo-Neustadt and colleagues have suggested that the combination of exercise and pharmacological antidepressant treatment exerts additive neurochemical changes that are superior to those induced by either treatment alone [21,22]. These data indicate that a combination of exercise and antidepressant medication enhances BDNF levels and subsequent monoaminergic activity.

Norepinephrine and serotonin

Exercise has been associated with increased activity in both noradrenergic and serotonergic systems, both of which have been extensively linked to depression. Studies of voluntary wheel running in rats have detected increases in levels of norepinephrine and metabolites such as 3-methoxy-4-hydroxyphenylglycol in the frontal cortex and hippocampus, and increased extraneuronal metabolism of norepinephrine [23,24]. Investigation of norepinephrine release and turnover in vivo during treadmill running using microdialysis techniques has revealed increases during exercise [25,26]. In addition, wheel running and treadmill training have been associated with changes in neuropeptides that modulate noradrenergic activity, such as galanin, in the locus coeruleus [27].

With respect to the serotonergic system, exercise – treadmill running in particular – has been shown to increase serotonin release [18,28–30]. Exercise has also been associated with increased levels of 5-hydroxyindoleacetic acid (5-HIAA), the main metabolite of serotonin, in the cortex, hippocampus, hypothalamus, striatum, and brainstem [31,32]. Neuroendocrine challenge studies suggest that physical activity results in the down-regulation of postsynaptic serotonin receptors, specifically serotonin 5-HT2C receptors, which may be relevant to both depression and anxiety [33,34]. Although more studies are needed in this domain, a variety of approaches have indicated that exercise influences noradrenergic and serotonergic neurotransmission, supporting the use of exercise as a treatment for depression – a disorder associated with alterations in these neuromodulatory systems.

Phenylethylamine

The monoamine phenylethylamine may play a role in the antidepressant effect of exercise. Phenylethylamine has been linked to the regulation of mood [40], and levels of phenylethylamine have been found to be reduced in depressed persons [35]. Phenylethylamine inhibits the reuptake of norepinephrine, acting in the same manner as the norepinephrine reuptake inhibitors, a class of pharmacological agents commonly prescribed as antidepressants. This mechanism of action may explain how increased levels of phenylethylamine could alleviate depressive symptoms, although this theory remains to be tested.

A study by Szabo et al. revealed that exercise increases levels of phenylacetic acid, the metabolite of phenylethylamine, in healthy, physically active men [36]. Although caution must be taken with respect to how generalizable these findings are, they provide support for a link between phenylethylamine and exercise. With the increasing number of studies of this nature, we may gain more specific neuropharmacological support for the mechanisms by which exercise elicits antidepressant effects. The existing evidence provides converging support from multiple neurochemical processes that endorse the use of exercise as an antidepressant therapy. Table 1 summarizes some of the most relevant findings.

Exercise and bipolar disorder

There has been very little investigation into the possible benefit of exercise in patients with bipolar disorder. One study examined exercise and nutrition behaviors in individuals diagnosed with bipolar disorder, schizophrenia, or no serious mental illness who participated in the Veterans Affairs Large Health Survey of Veteran Enrollees [41]. Individuals diagnosed with bipolar disorder were more likely to report suboptimal exercise habits than those diagnosed with schizophrenia or those with no serious mental illness, with respect to both walking (odds ratio [OR] 1.33; p<0.001) and strengthening exercise (OR 1.28; p<0.001).

A recent pilot study evaluated symptoms in inpatients diagnosed with bipolar disorder who elected to regularly participate in a walking program in addition to their ongoing treatment [42]. The 21-item version of the Depression Anxiety Stress Scales (DASS), a self-report measure, was used to evaluate symptoms, along with the clinician-rated Clinical Global Impression (CGI) scale. The duration of participation varied according to the length of participants’ admission. Regular participants in the walking program had significantly lower DASS scores (total and subscales) than did non-participants (p<0.05), although neither CGI improvement nor CGI severity were significantly different between groups. These data indicate a need for further evaluation of the benefits of exercise in individuals suffering from bipolar disorder.

Additional benefits of exercise in individuals with mood disorders

In addition to improvements in symptoms, exercise provides a variety of benefits that enhance its value in the treatment
of individuals with mood disorders, such as improvements in blood pressure [43] and reduced risks of coronary disease [44,45], stroke [46], diabetes [47,48], and various cancers [49,50]. These benefits are of particular importance given the significant comorbidity of mood disorders with cardiovascular disease and other significant health conditions.

Furthermore, exercise has a beneficial effect on some of the symptoms of depression that frequently remain despite antidepressant treatment, i.e. residual complaints such as impairments in cognitive function, fatigue, and insomnia. Exercise has been associated with improvements in cognitive functioning [51–54], which may make it an ideal option for the treatment of depressed individuals with cognitive complaints. Furthermore, exercise has been associated with increases in quality of life, functioning, and longevity [49,55].

### Psychological and psychosocial factors influencing exercise as a treatment for mood disorders

When considering the use of exercise as a treatment for mood disorders, it is important to evaluate the reciprocal influence of psychological and psychosocial factors on physical activity. There has been a significant focus on a variety of such factors as they relate to the adoption and maintenance of physical activity [56] (see Marcus et al. 2000 for a review). The development of physical activity interventions has been heavily influenced by two main theoretical models: the Transtheoretical Model (TTM; also known as “Stages of Change”) [57] and social cognitive theory [58]. These two models have equipped investigators with important constructs to be considered when evaluating the efficacy of physical activity interventions.

The TTM describes five stages involved in the adoption of physical activity as follows:

- **Precontemplation** – no intent to change behavior within 6 months.
- **Contemplation** – intent to change behavior within 6 months.
- **Preparation** – minimal or inconsistent changes in behavior.
- **Action** – active involvement in a behavior for <6 months.
- **Maintenance** – sustained behavioral change for ≥6 months.

When using a stage-model approach to intervention design, there are many factors that are evaluated and monitored throughout the process of adopting a behavior, including readiness to change, contributors to stage transition, and stage-targeted strategies that target behaviors and issues specific to that stage. For example, studies have shown that targeting specific exercise behaviors, such as setting goals [59] or monitoring self-efficacy [60], can increase the likelihood of progression to the next stage of change. For this reason, many exercise interventions have been designed using a stage-targeted approach to increase the likelihood of increasing physical activity behaviors [61,62]. In addition, determinants such as mastery (or the degree of control over one’s disease), behavioral processes related to change (e.g. rewarding oneself) [63], knowledge of risks and benefits, expectations of outcome, and perceived barriers and benefits [64] can be important considerations in the evaluation of the effectiveness of an exercise intervention on disease outcomes.

Research on factors important in the adoption and maintenance of physical activity has led to the development of multicomponent approaches to exercise interventions, incorporating processes such as developing a specific action plan for activity and targeting barriers to completion of the activity. These processes serve to increase the likelihood of adherence and provide flexibility (i.e. multiple possibly effective strategies) to cater for the different needs of the individuals undertaking the exercise regimen [65,66]. Such flexibility is particularly needed for psychiatric populations, where psychological aspects of the disease process may increase barriers to exercise or make it difficult to move on to the next stage of behavioral change. The evaluation and management of these barriers is likely to be relevant to the evaluation of the efficacy of an exercise intervention in patients with mood disorders.

In addition to considering psychological and psychosocial factors as they relate to the implementation of and adherence to exercise, it is important to evaluate the possibility that mood improvement is based on, or at least

### Table 1. Neurochemical systems relevant to depression that are altered by exercise.

<table>
<thead>
<tr>
<th>Neurochemical system</th>
<th>Summary of effects of exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonin</td>
<td>Increased levels of 5-HIAA</td>
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<tr>
<td></td>
<td>Increased serotonergic release</td>
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<tr>
<td></td>
<td>Down-regulation of 5-HT2C receptors</td>
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<tr>
<td>Norepinephrine</td>
<td>Increased norepinephrine turnover</td>
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<tr>
<td></td>
<td>Increased norepinephrine release</td>
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<tr>
<td></td>
<td>Changes in neuropeptides that modulate NE activity</td>
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<tr>
<td>BDNF</td>
<td>Increased BDNF mRNA, particularly in the hippocampus</td>
</tr>
<tr>
<td>Phenylethylamine</td>
<td>Increased levels of phenylacetic acid, the metabolite of phenylethylamine</td>
</tr>
</tbody>
</table>

5-HIAA: 5-hydroxyindoleacetic acid; 5-HT2C: serotonin 2C; BDNF: brain-derived neurotrophic factor; NE: norepinephrine.
enhanced by, improvements in determinants such as self-efficacy. A study by Lewis et al. reviewed psychosocial mediators of physical activity behavior, including behavioral processes of change (e.g. rewarding oneself, enlisting social support), cognitive processes of change (e.g. increased knowledge, comprehension of benefits), self-efficacy, decisional balance (i.e. weighing pros and cons), social support, and enjoyment [63]. The results indicated that behavioral processes of change, and to a lesser extent self-efficacy, are mediators by which exercise interventions increase physical activity behavior. Thus, the extent to which these factors change in patients with mood disorders who participate in an exercise intervention may directly or indirectly affect the efficacy of the intervention, and may certainly be relevant to the maintenance of physical activity after the intervention is completed.

It is possible that exercise may improve mood and anxiety simply because it serves as a distraction from negative cognitions or affect. Such a hypothesis has been tested in the context of exercise and a reduced desire to smoke [67]. Desire to smoke and symptoms of withdrawal, including depression, were measured following either 10 min of moderate exercise or a cognitive distraction task. Desire to smoke and all withdrawal symptoms were significantly lower during exercise than during the cognitive distraction task. However, there were no differences between groups with regard to depression, tension, or restlessness following the interventions, although the study was not conducted in depressed individuals. These findings suggest that distraction is not likely to be responsible for the reductions in the desire to smoke and many of the withdrawal symptoms, but further investigation of this potential relationship is necessary in research into both smoking and mood disorders. Future research evaluating the effect of exercise on mood should account for a potential relationship between psychological and psychosocial processes and mood improvement, and should consider these factors when evaluating outcomes.

Clinical use and research design recommendations
Although more well-controlled research is clearly needed to better understand how to use exercise as a treatment for mood disorders in clinical practice, there are some practical guidelines that clinicians can begin to use based on the existing research. Firstly, the amount of exercise consistent with current public health dose guidelines, i.e. approximately 30 min/day on most days of the week, appears to be helpful in reducing depressive symptoms. Secondly, physicians should encourage the use of supervised or group exercise to facilitate adherence to an exercise program. Thirdly, encouraging patients to track their exercise behavior is helpful to ensure continuation (see Trivedi et al. [16] for an example of an exercise log).

Future research in this area will benefit from the increase in well-designed trials that include clinical interviews to establish diagnoses, concealed treatment allocation, blinded evaluation of outcome measures, and use of intention-to-treat analyses. Future clinical trials should aim to better define the amount and types of exercise that are beneficial to patients with mood disorders, and long-term follow-up studies should be carried out to determine the potential of exercise to prevent relapse and recurrence of depressive episodes. Evaluation of the impact of relevant treatment mediators such as age, gender, fitness level, and body mass index is needed. In addition, it will also be important to evaluate how response and neural changes associated with exercise in mood disorders are reciprocally affected by psychological and psychosocial variables. Certainly, more investigations assessing the impact of exercise on bipolar disorder are needed, as well as studies that focus on the relationship between exercise and specific residual symptoms of depression, such as cognitive function. In addition, translational research that bridges preclinical and clinical research will significantly enhance our understanding of the effect of exercise on mood disorders and should be a focus of future research in this area.

Conclusion
Converging preclinical and clinical data suggest that exercise can benefit individuals with mood disorders. Neurobiological studies have revealed that exercise alters neural systems involved in depression and its treatment. Cohort studies show an inverse relationship between physical activity and depressive symptoms, and an increasing number of efficacy studies are providing support for the utility of exercise as a treatment for mood disorders. Methodological issues have limited much of the previous research in this field; however, newer, more rigorously controlled studies are being conducted and will help us to better understand how exercise can benefit patients with mood disorders.

Disclosures
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References
Augmentation of antidepressants with atypical antipsychotic medications for treatment-resistant major depressive disorder: a meta-analysis


In this pooled analysis of 10 trials of augmentation treatment with atypical antipsychotic medications, patients with treatment-resistant major depressive disorder receiving a study drug showed improved rates of response and remission compared with those given placebo.

Treatment of major depressive disorder (MDD) is limited by non-response in a sizeable number of individuals receiving therapy, and residual depressive symptoms remain even in some patients categorized as medication responders. A number of augmentation strategies for depression treatment have been investigated, with lithium and thyroid hormone being among the most commonly studied. Atypical antipsychotic medications have receptor-binding profiles that suggest potential antidepressant effects; thus, this class of medications is frequently used as an augmentation strategy in patients with treatment-resistant MDD. Papakostas and colleagues performed a literature search in order to identify double-blind, placebo-controlled trials of a typical antipsychotic medications used to augment antidepressant treatment in patients with MDD. They analyzed the pooled response, remission, and discontinuation rates of the atypical antipsychotic augmentation group compared with the placebo add-on group.

Ten acute treatment trials involving a total of 1500 outpatients were included in the analysis. Five studies focused on olanzapine, three on quetiapine, and two on risperidone; due to the timing of this study, aripiprazole and ziprasidone were not included. Olanzapine was added to fluoxetine in all the five studies of this drug, while quetiapine and risperidone were used to augment a variety of antidepressants. The methodologies of the trials identified varied, with differences including study duration (4–12 weeks), sample size (15–303 individuals), primary rating instruments (Montgomery Asberg Depression Rating Scale or the 17-Item Hamilton Depression Rating Scale), and remission criteria. Response criteria were all standardized as a ≥50% improvement.

Pooled response and remission rates were higher for the atypical antipsychotic augmentation groups compared with the placebo add-on groups (57.2% and 47.4% vs. 35.4% and 22.3%, respectively [p=0.001 and p<0.001, respectively]). The overall pooled discontinuation rates were similar between groups, but discontinuation rates due to adverse events were higher in the treatment groups (p<0.0001).

Standard care for patients with treatment-resistant MDD includes augmentation with atypical antipsychotic medications. The results of this study support such practice, even though no agent in this medication class is currently approved for this use. However, the non-inclusion of the two newest medications in this class, aripiprazole and ziprasidone limits the study findings. Augmentation with olanzapine was also over-represented (1017 of the 1500 patients), and this effect was further amplified by analysis using pooled response and remission, rather than effect size. The use of pooled analysis instead of effect sizes allowed studies with greater sample sizes to have a greater impact on the results of this study, which must be considered in light of the varying study methodologies (such as inclusion, exclusion, and remission criteria). Finally, patients in these 10 studies were non-representative subjects selected to participate in rigid clinical trials, and thus may not resemble typical clinical outpatients. Nevertheless, these results echo and support the common clinical practice of using a typical anti-psychotic medications to augment standard antidepressant medications in the care of patients with treatment-resistant MDD.

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The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study

Berman RM, Marcus RN, Swanink R et al.


Adjunctive aripiprazole is effective at improving response and remission rates in treatment-resistant patients with major depressive disorder.

Despite a wide range of antidepressant medication options for patients with major depressive disorder (MDD), a substantial proportion fails to experience response or remission. Atypical antipsychotic medications have receptor-binding profiles that suggest antidepressant efficacy, and a recent meta-analysis of atypical antipsychotic medication add-ons to standard antidepressant medications found enhanced rates of response and remission [1; reviewed here on p166]. Berman and colleagues examined the efficacy of aripiprazole as an adjunctive therapy for patients with treatment-resistant MDD (lack of response to 2–4 trials of antidepressant in the current depressive episode).

A total of 362 subjects with MDD were randomly assigned to treatment with adjunctive placebo or aripiprazole (mean dose 11.8 mg/day, range 2–20 mg/day), added to selective serotonin reuptake inhibitors or venlafaxine, for 6 weeks. On the primary efficacy measure, the Montgomery–Asberg Depression Rating Scale (MADRS), scores showed a significantly greater decrease in the aripiprazole-treated patients (8.8 points) than in those receiving placebo augmentations (5.8 points). This decrease was observed by week 2. Response and remission rates were also significantly higher with active treatment compared with placebo augmentation by the end of the study (33.7% vs. 23.8% and 26% vs. 15.7%, respectively [p=0.027 and p=0.011, respectively]).

Aripiprazole was generally well tolerated in the study, with low discontinuation rates due to adverse effects (2.2% for aripiprazole and 1.7% for placebo). The most common adverse events for aripiprazole-treated patients were akathisia (23.1%) and restlessness (14.3%).

In this large, randomized, parallel-group, placebo-controlled study, adjunctive aripiprazole improved response and remission rates for treatment-resistant MDD, and was well tolerated. Furthermore, effects were noted as early as week 2. Although these findings were significant in this sample of patients with MDD, two recently completed monotherapy studies in patients with a major depressive episode in the context of bipolar I disorder failed to show statistical separation from placebo [2]. Interestingly in the bipolar depression study, statistical separation was noted at the 6-week timepoint of the study, but not at the study endpoint of 8 weeks. In both the MDD and bipolar depression studies, improvement emerged early in treatment. Whether aripiprazole has benefits in speeding antidepressant response but loses efficacy after prolonged treatment (>6 weeks) requires further study.


2. Marcus RN, Owen R, Swanink R et al. Two studies to evaluate the safety and efficacy of aripiprazole monotherapy in outpatients with bipolar I disorder with a major depressive episode without psychotic features (Studies CN138-096 and CN138-146), American Psychiatric Association 160th Annual Meeting 2007. San Diego, CA, USA.

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Decline in treatment of pediatric depression after FDA advisory on risk of suicidality with SSRIs

Libby AM, Brent DA, Morrato EH et al.


A public health advisory was issued by the US Food and Drug Administration (FDA) in October 2003 about the risk of suicidality in children taking selective serotonin reuptake inhibitors (SSRIs) for the treatment of depression. The authors of the present study examined the patterns of the diagnosis of depression, prescriptions for various pharmacological treatments (including SSRIs), and the use of psychosocial care, before and after the FDA advisory, in a large national cohort of pediatric patients. The results indicate that after the advisory the rates of diagnosis and treatment of depression in children, particularly in primary care, were significantly reduced.

Depression in young people has been associated with poorer health and development, and lower economic advancement in later years. Prior to the “black box” warning concerning the increased suicidal risk in pediatric patients treated with selective serotonin reuptake inhibitors (SSRIs) for depression, the US Food and Drug Administration (FDA) issued a public health advisory in October 2003 containing similar warnings.

The aim of this study was to evaluate the effect of this advisory on the diagnosis of depression in children, the prescription of antidepressants (including SSRIs) and other pharmacological treatments for depression in this population, and the use of psychosocial care in those diagnosed with depression.

Data were obtained from the PharMetrics Patient-Centric Database (PharMetrics, Watertown, MA, USA), which includes information on 85 managed care plans in the USA, covering 47 million people. Data were extracted for patients who had a new diagnosis of either a major depressive disorder or a related psychiatric disorder, or had a paid claim...
for a filled prescription for an antidepressant medication. Information on 541,187 new episodes of depression were identified, and of these, 65,349 cases of new-onset depression in subjects aged 5–18 years were examined. Data for the 2 years following the FDA advisory were compared with “expected” values predicted by modeling data from the 5 years previous to the advisory.

The study revealed that from 1 January 1999 to 31 December 2004, there was an increase in the rate of new diagnoses of depression in the pediatric population, followed by a significant drop in diagnoses in 2005, a finding not accounted for by changes in population demographics. The majority of diagnoses made prior to the 2003 advisory were made by pediatricians and non-pediatric primary care physicians. After the 2003 FDA advisory, although pediatrician diagnoses of depression did not change, there was a substantial drop in those made by non-pediatric primary care physicians. In addition, the study showed that by September 2005, the proportions of diagnoses of depression by these two groups of physicians were both 32% lower than those predicted by data modeling of rates derived from 1999–2004. Over the course of this time, the percentage diagnoses of depressive episodes by psychiatrists increased by 3.39% annually, and by September 2005, the relative share of depression diagnoses by psychiatrists was 19% higher than that expected by modeling the data for the 5 years from 1999.

From October 1998 to the FDA advisory in October 2003, a mean of 59% of patients who were diagnosed with depression received an SSRI prescription, increasing by 1.9% per year during this time. After the advisory, the percentage of SSRI prescriptions decreased by 0.42% annually, with an average of 28% of depressive episodes currently being treated with SSRIs — substantially lower than the 67% rate predicted by modeling data from 1999–2004. The number of patients receiving no prescription for an antidepressant increased by 8.83 percentage points in the post-advisory period. While 19.36% of patients were predicted to have no antidepressant prescription based on modeling, the observed percentage in September 2005 was 63.7%. There was no change in the number of patients receiving at least one psychotherapy session; however, the rate of psychotherapy (40.3%) was higher than that predicted (30.7%). This study suggests that after the 2003 FDA public health advisory, there were significant reductions in the diagnosis and treatment of depression in children, particularly in primary care.

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Efficacy of duloxetine on cognition, depression, and pain in elderly patients with major depressive disorder: an 8-week, double-blind, placebo-controlled trial


This double-blind, placebo-controlled study examined the effects of duloxetine treatment in a cohort of 311 elderly patients with major depressive disorder. The results suggest that duloxetine improves depression, pain, and cognitive measures (primarily verbal memory and learning) in this group of patients.

Major depressive disorder (MDD) in the elderly has been associated with cognitive deficits and physical disability. Memory, focused attention, and learning are specific cognitive functions that may be particularly vulnerable to degradation as a result of depression. An imbalance in the neurotransmitters serotonin and norepinephrine has been shown to be involved in cognitive deficits, and the dual action of duloxetine hydrochloride may produce improvements. The authors of this multicenter, placebo-controlled, double-blind study explored the effects of duloxetine on pain, depression, and cognitive function in elderly patients with MDD.

In total, 311 elderly outpatients who met the criteria for recurrent MDD were randomized to receive duloxetine (n=207; 60 mg/day) or placebo (n=104) for 8 weeks. The severity of depression was assessed with the 17-item Hamilton Rating Scale for Depression (HAM-D17), and dementia status was assessed with the Mini-Mental State Examination (MMSE). A composite score of four cognitive tests (ranging from 0–51) was used as the primary outcome measure: the Letter-Number Sequencing Test, the Two-Digit Cancellation Test, the Symbol Digit Substitution Test, and the Verbal Learning and Recall Test. Secondary outcome measures included the Visual Analogue Scale for pain, the Clinical Global Impression severity scale, the Geriatric Depression Scale, and the HAM-D17.

The results revealed that composite cognitive scores showed a greater improvement in the duloxetine group than in the placebo group (least-squares mean change from baseline to the end of the study 1.95 vs. 0.76); verbal learning and memory were the components with the greatest contributions to this improvement. With regard to pain measures, the duloxetine group showed greater improvements in Visual Analogue Scale scores for back pain and time in pain than those in the placebo group data.

Subjects in the duloxetine group showed significantly greater improvements on both measures of depression...
compared with subjects taking placebo (reductions in HAM-D17 of 6.49 and 3.72 respectively, and the Geriatric Depression Scale of 4.07 and 1.34, respectively). Furthermore, subjects in the duloxetine group showed greater HAM-D17 scale response rates (37.3% vs. 18.6%) and remission rates (14.7% vs. 2.74%) than those in the placebo group. Although the incidence of adverse events resulting in discontinuation was similar in the two groups, fewer patients in the duloxetine group withdrew from the study due to lack of efficacy (2.9% vs. 9.6%).

These findings are limited by the fact that the study only measured variables up to the end of the 8-week treatment phase and excluded subjects with serious medical and psychiatric comorbidities.

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Open trial of family-based treatment for full and partial anorexia nervosa in adolescence: evidence of successful dissemination
Loeb KL, Walsh BT, Lock J et al.

The authors of this open trial investigated the use of family-based treatment (FBT) in manual form for anorexia nervosa in adolescents. In this trial of 20 adolescents, 65% of participants achieved a good outcome with FBT, suggesting that this treatment method can be successfully used at other facilities.

A family-based outpatient weight gain protocol for the treatment of patients with anorexia nervosa has been developed by the Maudsley Hospital (London, UK) and published as a manual. This approach is different to others in several ways. Family-based treatment (FBT) places the parents of the patients in charge of the initial weight restoration, and the independence of the patient is emphasized only after a substantial improvement is observed. Traditional treatments are usually more intensive and long-term, and often involve hospitalization. Rather than being based on a single treatment model, FBT uses a combination of models and stems from the assumption that the family is the best resource for treatment of anorexia nervosa in adolescents. The aim of this open trial was to investigate the efficacy of FBT in manual form for the treatment of anorexia nervosa in adolescents at a treatment facility other than that at which the protocol originated.

The authors recruited 20 adolescent subjects with sub-threshold or full anorexia nervosa as defined by DSM-IV criteria. All subjects were aged 12–17 years and had at least one parent willing to participate in treatment. In addition to weight gain, outcome measures included menstrual status, percentage of ideal body weight (%IBW), and Children’s Depression Rating Scale – Revised (CDRS-R) scores. The authors also used the Eating Disorders Examination (EDE), a semi-structured interview that assesses eating and inappropriate compensatory behavior along with concerns with eating, weight, and shape, and gauges the level of dietary restraint. This assessment tool is considered the gold standard for eating disorders.

Patients were treated with FBT in accordance with the published manual on the therapy. Subjects received 20 sessions over the course of 12 months in three phases. The first 10 sessions involved encouraging the parents to assume control over the patient’s weight and help restore it to a more healthy level. Once subjects have attained a minimum %IBW of 87%, they could enter the second phase of treatment, which involves the transition of control from the parent to the patient over six sessions. Once the patient is eating independently and serious symptoms of anorexia nervosa have improved substantially, the patient enters the third phase of therapy. In this final phase of the treatment, general concerns regarding adolescence and termination issues are addressed.

Patients were allowed up to 30 sessions, with the mean number of sessions for completion being 22.1. Overall, the %IBW improved over the course of the study from 82.30% to 93.61%, with statistical analysis revealing a large effect size. Improvements were also observed on the EDE eating concern and restraint subscales, but there were no improvements on the EDE weight concern or shape concern subscales. There was no significant change in CDRS-R score from baseline to termination. The percentage of menstruating female patients increased significantly, from 11% at baseline to 67% at the end of treatment. Overall, 65% of participants, including all seven patients with sub-threshold anorexia nervosa met established criteria for a good outcome. Regression analysis revealed that, compared with typical treatment intensity, incomplete treatment predicted lower %IBW at termination.

The present study suggests that FBT administered by healthcare professionals can be successfully utilized at treatment facilities other than those where the treatment was developed. Although these findings are promising, they are limited by the fact that the study was an open trial with no head-to-head comparisons with other treatments. The small number of participants also precludes the identification of criteria for the prediction of patients most likely to benefit from FBT.
EPIDEMIOLOGY

Epidemiology and characteristics of emergency departments visits by US adults with psychiatric disorder and antipsychotic mention from 2000 to 2004


The authors of this retrospective study investigated the epidemiology of psychiatric disorders and the characteristics of antipsychotic use in patients attending emergency departments (EDs) in the USA. ED patients associated with antipsychotic treatment were usually Caucasian adults aged <40 years, who were reimbursed by public-funded insurance schemes. Patients with a diagnosis of depression or bipolar disorder and those who prescribed a greater number of medications were more likely to receive atypical rather than typical antipsychotics.

Published expert consensus on the treatment of psychiatric disorder and mania in the emergency department (ED) supports the use of antipsychotic medications alone or in combination with a benzodiazepine; however, data on the use of atypical antipsychotic medications in adults in the ED is mostly limited to the control of behavioral emergencies and agitation. Decisions on US healthcare policy have previously been guided by the results of the National Hospital Ambulatory Medical Care Survey (NHAMCS) and the National Ambulatory Medical Care Survey. The NHAMCS gathers data from 50 primary sampling units, which include hospitals with EDs throughout the USA. The authors of this study investigated the epidemiology of psychiatric disorders in US EDs and the characteristics of antipsychotic use in these patients, using data for the years 2000–2004 from the NHAMCS database.

Antipsychotic medication mentioned in the database was categorized as being typical (TT), atypical (AT), or a combination of the two (CT). The authors report that 8% (2 million) of the 26 million psychiatric ED visits identified in the database were associated with a mention of antipsychotic medication (8% of these patients were in the CT group, 55% in the AT, and 38% in the TT). Between 2000 and 2004 all groups showed an increase in ED visits. More CT and TT visits versus AT visits mentioned medication for treatment of extrapyramidal symptoms (40%, 14% vs. 4%; p<0.0001). A greater proportion of CT and AT visits versus TT visits mentioned medication for treatment of convulsions (42% and 35% vs. 12%; p<0.0001) and depression (31% and 42% vs. 11%; p<0.0001). A higher likelihood of atypical versus typical antipsychotic medication was related to the diagnosis of depression (odds ratio [OR] 3.2), bipolar disorder (OR 2.5), and a higher number of medications received (OR 1.4). Of note, the majority of patients with a mention of antipsychotic medications were aged <40 years, Caucasian, required immediate treatment, and were ultimately reimbursed by a public insurance scheme.

The results suggest that AT and CT antipsychotic medications associated with psychiatric ED visits increased between the years 2000 and 2004. The findings of this study are limited by the NHAMCS data collection process, which is subject to errors in coding and record review. Data from surveys such as this often do not include all medications a patient is prescribed, which may result in an underestimation of the type and number of medications.

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 Depression and generalized anxiety disorder: cumulative and sequential comorbidity in a birth cohort followed prospectively to age 32 years


In a cohort of patients with comorbid major depressive disorder (MDD) and generalized anxiety disorder (GAD), MDD onset preceded GAD in one-third of patients, GAD onset preceded MDD in one-third of patients, and MDD and GAD had concurrent onset in the remaining one-third of patients. These data suggest that MDD and GAD should be re-conceptualized as co-equal contributors to a new nosological entity, rather than GAD being incorporated into the MDD diagnostic entity.

The validity of the syndrome of generalized anxiety disorder (GAD) has been questioned. A high proportion of patients (two-thirds) with an initial diagnosis of GAD go on to develop major depressive disorder (MDD); GAD is therefore thought to be a prodromal state of MDD. In contrast, only one-fifth of MDD patients report a prior history of GAD, suggesting that MDD is a separate entity from GAD. With the impending development of the next edition of the Diagnostic and Statistical Manual of Mental Disorders, this nosological dilemma requires clarification. The present authors examined 1037 members of the Dunedin cohort of 1972–73 [1] for diagnoses of anxiety and depression at the ages of 11, 13, 15, 18, 21, 26, and 32 years, in order to assess the sequential development of anxiety and depression diagnoses.

Overall, a lifetime prevalence of MDD by the age of 32 years was approximately 20% in women, close to double the rate of MDD seen in men. MDD in childhood was
relatively low, with the greatest rise in prevalence occurring between the ages of 15 and 18 years for both men and women. Women had higher rates of anxiety disorders than men. In contrast to MDD, anxiety disorders were already present at the earliest follow-up of 11 years of age.

Analysis of the prevalence rates of MDD and GAD for adults (18–32 years old) found that 12% had comorbid MDD and GAD, 22% had MDD alone, 2% had GAD alone; only 23% had no psychiatric diagnosis. Considering only the group with comorbid MDD and GAD in adulthood, the sequential onset of MDD or GAD was divided into approximately equal thirds: one-third had first onset of MDD, one-third had first onset of GAD, and one-third had concurrent onset.

The analyses from this cohort suggest that GAD is not just a subset of MDD, but that MDD and GAD may share similar developmental processes. Prior literature suggested that GAD may be a prodrome to MDD, but this analysis supports the re-conceptualization of MDD and GAD as co-equal contributors to a new combined nosological entity, proposed as a “distress category”, by the authors. This classification would also be more in keeping with the current standards of treatment.

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Increased rates of bipolar disorder diagnoses among US child, adolescent, and adult inpatients, 1996–2004

Blader JC, Carlson GA.

Between 1996 and 2004, the number of children, adolescents, and adults diagnosed with bipolar disorder increased by 420%, 300%, and 56%, respectively. However, a number of confounding factors may mitigate some of this increased prevalence in hospital discharges, beyond just an increase in the clinical phenomenology.

A contemporary clinical question concerns whether bipolar disorder is under-recognized or over-diagnosed. Blader and Carlson examined this issue using data from the annual National Hospital Discharge Survey, supplied by the US Centers for Disease Control and Prevention (CDC), which provides data to the public at ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Datasets/NHDS.

Between 1996 and 2004, hospital discharges with a primary discharge diagnosis of bipolar disorder increased linearly, and at a greater rate in children and adolescents compared with adults. Population-based rates increased by 420% in children, 300% in adolescents, and 56% in adults. Overall, population-based rates of discharges with psychiatric diagnoses increased considerably between 1996 and 2004 in children (53% increase) and adolescents (59% increase), but not in adults (3% increase). Thus, the proportion of hospital discharges with a bipolar disorder diagnosis increased more than that of psychiatric disorders in general. Among secondary discharge diagnoses, substance abuse disorders were predominant in both adolescents and adults (81% of the secondary diagnoses), whereas children did not have a predominant secondary diagnosis category.

Taken at surface value, the prevalence of diagnoses of bipolar disorder seem to have increased by an extraordinary amount between 1996 and 2004, rising from an infrequent discharge diagnosis in 1996 to the most frequent discharge diagnosis among psychiatric disorders in 2004. However, several significant factors need to be considered. Importantly, these data represent discharge diagnoses. The same individual may be counted more than once in the dataset if the same person required more than one hospitalization. These data were also collected during a period of increasing payer vigilance in which payments were only made for the most acute cases that could not be managed in the outpatient setting. Hospitalizations were justified to payers for treating more severe mental illness or may have led to possibly clinically “up-coding” of diagnoses to more severe disorders, even in the face of similar clinical phenomena in 1996 and 2004. What may have been classified as conduct or school problems in 1996 may have been coded as bipolar disorder in 2004 for reimbursement purposes. In addition, between 1996 and 2004, the number of bipolar medications approved by the US Food and Drug Administration increased from three to 11, possibly providing a greater clinical rationale to diagnose bipolar disorder. With each of these situations, the clinical phenomena would not have changed in the community as a whole, but the hospitalization data would have become skewed toward greater rates of bipolar disorder. Finally, these discharge diagnoses do not reveal the stringency of adherence to diagnostic criteria for bipolar disorder; frequently, volatile or aggressive behavior alone may be enough to code a bipolar disorder diagnosis without meeting the full DSM-IV criteria. Although bipolar disorder is clearly diagnosed more frequently, the extent to which the clinical phenomena of bipolar disorder – as studied for research purposes – has become more prevalent in the community as a whole requires further investigation.

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 Hippocampal volume and subcortical white matter lesions in late life depression: comparison of early and late onset depression


Hippocampal atrophy is associated with early-, but not late-onset depression, suggesting that a more recurrent type of this illness may be associated with the pathophysiology of hippocampal atrophy seen in depression.

Hippocampal atrophy has been associated with a more chronic course of illness in major depressive disorder (MDD). Subcortical white matter lesions have also been associated with MDD. The authors sought to differentiate these pathological findings between subjects with early-onset depression (EOD), late-onset depression (LOD), and healthy controls (HC).

Thirteen patients with EOD (first onset of depression aged <60 years), 15 patients with LOD (first onset of depression aged ≥60 years), and 22 HC subjects, all female and aged ≥60 years, underwent 1.5-Tesla T1 and T2 magnetic resonance imaging brain scans. Hippocampal volumes were normalized to total brain volumes. Subcortical white matter lesions were grouped by size into small or large, and tallied.

Even after adjusting for age and score on the Mini-Mental State Examination, patients with EOD had smaller mean hippocampal volumes than HC subjects (5.51 mL vs. 6.0 mL; p=0.04), and numerically, but not statistically, smaller mean hippocampal volumes than LOD patients (5.92 mL; p=0.16). Patients with LOD had a hippocampus of a similar size to the HC subjects. Patients with LOD had a significantly greater number of large, but not small, subcortical white matter lesions compared with EOD and HC subjects.

Prior studies have suggested that smaller hippocampal volumes are associated with recurrent depressive illness, possibly related to the neurotoxic effects of recurrent stress. The finding of smaller hippocampal volumes in patients with EOD compared with HC subjects is in line with previous literature. LOD is also thought to be related to cerebrovascular disease processes and to affect hippocampal volumes [1]; however, this finding was not repeated here. The authors suggest that the finding of a greater number of large subcortical white matter lesions in LOD patients may be an initial step in the pathophysiological process for this type of depression, although this would not explain the lack of significant findings with smaller subcortical white matter lesions. Due to the small sample sizes and the lack of statistical corrections for multiple comparisons, these latter findings will need replication.


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COMORBIDITIES

Hospitalization for depression is associated with an increased risk for myocardial infarction not explained by lifestyle, lipids, coagulation, and inflammation: the SHEEP Study


Prior hospitalization for depression is a significant risk factor, comparable to smoking, for the subsequent development of coronary artery disease. This increased risk is not fully explained by commonly known comorbidities such as lifestyle, lipid profile, coagulation, and inflammatory markers.

Depression has been studied as a risk factor for coronary artery disease (CAD) for many years, yet the specific linkage (lifestyle, lipid profile, coagulation, inflammatory markers, heart rate variability) remains to be determined. Prior studies have found that depression after a myocardial infarction is one of the most accurate predictors for a subsequent cardiac event. Depression has also been shown to predict the subsequent occurrence of CAD; however, the most recent American College of Cardiology task force statement on cardiac event prevention did not include depression as a risk factor. Janszky and colleagues sought to use longer term follow-up and a more concrete definition of a major depressive episode to investigate depression as a risk factor for subsequent development of CAD, correcting for other known risk factors.

Using data from participants in the case–control study SHEEP (Stockholm Heart Epidemiology Program), 1799 patients who had experienced a first episode of acute myocardial infarction (AMI) and 2339 controls, matched for age, gender, and hospital catchment area, were identified. Forty-seven patients and 22 controls had a prior history of psychiatric hospitalization for depression. The odds ratio (OR) for an AMI after hospitalization for depression was 2.9; this was comparable to the increased risk for the
development of CAD mediated by smoking. Even after adjusting for covariates (lipid levels, coagulation, inflammatory measurements, diabetes, hypertension, obesity, physical inactivity, smoking, alcohol, socioeconomic status, and sleep problems), the risk of CAD was higher in patients who had a prior hospitalization for depression.

A greater severity of depression was associated with an increased risk of developing CAD. Patients with psychotic depression (OR 5.0) or ≥3 hospitalizations for depression (OR 6.8) had the highest risk for an AMI.

In contrast with other studies, this investigation captured a large sample, and likely – given the health care system studied – included all subjects in the selected community. In addition, the definition of depression was stringent, with psychiatric hospitalization for this disorder being the required criteria. The findings showed that the associated risk between CAD and depression remains even after correcting for several known common comorbidities.

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**Stroke: a randomized trial of exercise or relaxation**

Mead GE, Greig CA, Cunningham I et al.


This 12-week interventional study investigated the feasibility of exercise training in patients who have recently suffered a stroke. Some additional benefits of exercise training compared with relaxation therapy were reported.

Although patients who have suffered a stroke often have reduced aerobic fitness, the effect of exercise training in this population has not been fully established. The aim of this randomized, controlled study was to investigate the efficacy and feasibility of exercise training in patients who have recently had a stroke. The authors enrolled 66 patients who had suffered a stroke and who had been discharged from hospital after completing a rehabilitation program. None of the subjects had any significant medical contraindication to exercise training and none had significant confusion or dysphasia. Participants were randomized to receive either relaxation treatment in the form of attention control or exercise training in the form of progressive resistance and endurance over 12 weeks. Both groups attended three sessions per week, each lasting 1 h and 15 min (including discussion), in sets of seven participants. Subjects in the exercise group underwent a program based on the Falls and Exercise Management Study, with exercise duration and intensity increased when the instructor perceived the subject was ready. The relaxation sessions included deep breathing and progressive muscle relaxation, with their duration increasing as the study progressed. Several screening tools were used to screen for functional independence, mental health, and physical health at baseline, including the Hospital Anxiety and Depression Score and The Functional Independence Measure. Subjects were reassessed at the end of the interventions (approximately 3 months), then 4 and 7 months later.

Of the 34 subjects who entered the relaxation group, 17 (50%) attended all sessions (≥36 sessions), while 17 subjects (59%) of the 32 participants in the exercise group attended all sessions. The study revealed that after 3 months, the subjects in the exercise group had significantly better timed “up-and-go”, walking economy, and role-physical measures than those in the relaxation group. At 7 months, only the role-physical measure was better in the exercise group. During the course of the intervention, eight of 32 patients in the exercise group experienced 11 falls in total, and four of 34 patients in the relaxation group reported a total of five falls.

This study suggests that exercise training in patients who have suffered a stroke is a feasible treatment option following conventional rehabilitation, with the exercise group showing some benefit in performance compared with the relaxation group. The findings are limited by the low percentage of patients who attended all the study sessions, and failure to measure the severity of stroke and pre-stroke function.

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**PROGNOSIS**

**Suicide attempts among patients starting depression treatment with medications or psychotherapy**

Simon GE, Savarino J.


The authors of this retrospective study analyzed the incidence of suicide attempts in patients with depression before and after the initiation of treatment with medication or psychotherapy. The results indicate that the highest number of attempts occurred in the month prior to treatment initiation and that the time pattern observed is not related to medication.

The US Food and Drug Administration issued a “black box” warning on antidepressant drugs, recommending the close monitoring of suicide ideation after these medications are
CLINICAL REVIEWS

initiated. Results have suggested that the incidence of suicide attempts and completed suicides is higher in the first weeks of treatment with antidepressant medication [1]; however, additional research has indicated that the risk of suicide attempts may be higher prior to treatment initiation [2]. This may be because patients often begin treatment during a time of crisis, when levels of suicidal ideation and other symptoms of depression are high, and these levels may decrease regardless of the treatment modality used.

The authors of the present study examined suicide attempts before and after starting treatment for depression with either psychotherapy or medication. Outpatient claims from a large US healthcare plan that includes 500,000 members were screened for new prescriptions for the treatment of depression. Subjects who had received initial antidepressant medication treatment from a psychiatrist or primary care specialist or a first psychotherapy visit were included in the original cohort. The same database was used to identify suicide attempts before and after the beginning of treatment.

The data showed that 109,256 individuals were treated during 131,788 episodes of depression. Of these treatment episodes, 40% began with a psychotherapy visit, 55% began with a prescription for an antidepressant in primary care, and 5% began with a prescription for an antidepressant by a psychiatrist. In total, 715 suicide attempts were identified over the 90 days prior to and the 180 days after treatment initiation. Suicide attempts occurred most frequently among patients prescribed antidepressant medication by psychiatrists, followed by patients initiating psychotherapy with a psychiatrist, and antidepressants prescribed by primary care physicians. For all three groups, the highest number of suicide attempts occurred in the month before starting treatment, the next highest were observed in the month immediately after starting treatment, and the number decreased thereafter. These findings persisted even after accounting for patients receiving overlapping medication and psychotherapy, and suggest that the pattern of suicide attempts in the time before and after treatment initiation is not specific to medication. Secondary analysis of patients aged <25 years revealed that, while the time pattern remained the same, the incidence of suicide attempts was twice as high as that in the group as a whole.

This study is limited by the fact that the severity of depression was not directly examined, and there was a high rate of patient drop-out from treatment, making it more difficult to identify treatment-specific effects.


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This double-blind, placebo-controlled study of 42 healthy subjects reports that the β-adrenoceptor antagonist propranolol prevents retrieval deficits induced by elevated glucocorticoid levels.

Research has shown that increased glucocorticoid levels increase long-term retention of memory of recent events, but reduce the ability to retrieve emotional information [1,2]. Animal studies suggest that the reduced information retrieval is mediated through noradrenergic transmission [3,4]. In this double-blind, placebo-controlled study, the authors examined the ability of the β-adrenoceptor antagonist propranolol to block glucocorticoid-induced impairments in memory consolidation of emotionally arousing words.

In total, 42 healthy volunteers were recruited into the study. On the first day of the study, participants were presented with a list of 60 unrelated nouns of varying emotionality for memorization. On the second day, participants were randomized to receive 40 mg of propranolol, 25 mg of cortisol, or both medications, and 1 h later wrote down all the words they could remember from the previous day. In each study group (n=14), 50% of the subjects received the designated medication; the remainder received placebo. After a 2-week washout period, the experiment was repeated with a different set of words, and those that received medication in the previous round received placebo and vice versa. Saliva levels of cortisol were assessed 1 h after the administration of the study medication and immediately before the recall test.

In subjects receiving cortisone, cortisol levels approximated those observed during psychological stress. Free recall of all words was delayed in those receiving cortisone compared with placebo (20.6 words vs. 24.6 words, respectively). When the recall of words according to category of emotional arousal was analyzed, it was revealed that cortisone inhibited retrieval of words designated as causing high emotional arousal by 42% (p=0.0001), but there was no impairment in the retrieval of words of medium or low emotional arousal. Drug effect did not show an interaction with gender or positive or negative valence of the word. In the group that received propranolol plus cortisone, cortisol levels were comparable to those seen in the subjects that received cortisone alone. In this group, subjects did not show impairments in memory retrieval of any category of words compared with placebo. Subjects receiving propranolol showed no appreciable increase in salivary cortisol levels and no reduction in memory recall of words in any category of emotional arousal.

The results of this study suggest that administration of propanolol can attenuate the inhibition of recall by high cortisol levels. This offers evidence that propanolol may have clinical utility in preventing memory deficits in depression, which is associated with chronically elevated glucocorticoid levels.


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Use of antidepressants and rates of hip bone loss in older women: the study of osteoporotic fractures
Diem SJ, Blackwell TL, Stone KL et al.

Selective serotonin reuptake inhibitor (SSRI) antidepressants, but not tricyclic antidepressants, are associated with a greater bone density loss than is observed in subjects who are not using an SSRI.

Recent literature has localized serotonin transporters in bone cells (osteoblasts, osteoclasts, and osteocytes) [1,2], suggesting that serotonin transporters may have some role in bone metabolism. Diem and colleagues sought to examine the effect of antidepressant medications on bone metabolism by measuring bone mineral density (BMD) at two separate visits (mean of 4.9 years apart) in 2722 older adult women (mean age 78.5 years) who were participating in the Study of Osteoporotic Fractures. BMD changes were compared in subjects who were using selective serotonin reuptake inhibitor antidepressants (SSRIs), tricyclic antidepressants (TCAs), or neither a SSRI nor a TCA (non-user) at either visit.

Over the follow-up period, subjects using SSRIs had statistically greater BMD loss (0.82% per year, p<0.001 compared with non-users) than either the TCA users (0.47% per year) or non-users (0.47% per year), with differences remaining significant even after adjusting for severity of depression at the baseline measurement visit.

A number of investigations have suggested that the use of SSRI antidepressants is associated with bone loss and greater risk of fractures; this study is supportive of these findings; however, an alternative explanation is that depression itself (possibly due to involvement of the hypothalamic–pituitary–adrenal system and stress steroids) or the sequelae of depression (decreased mobility and poor nutrition) leads to bone loss. This study did not address the issue of SSRI antidepressant use as the cause of decreased BMD, as use of antidepressant medications and the degree of depression during the follow-up period were not ascertained. Although TCA use may be considered an active control group, TCAs are often used for hypnotic effects, rather than antidepressant utility, making them inadequate for active comparison. Nevertheless, the association between SSRI use and bone loss and fractures appears to exist, and the next important issue is to determine the underlying mechanisms of this association.


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The congresses of the European College of Neuropsychopharmacology (ECNP) have become a major forum for scientists from all over the world to present their latest findings in neuropsychopharmacology and its related disciplines. The most recent meeting, the 20th ECNP Congress, took place from 13–17 October, in Vienna, Austria. The Scientific Programme Committee put together a high-caliber and well-balanced program covering developments in all of the major fields in this area. The purpose of this report is to summarize the most relevant data of interest to the journal reader. Abstracts have been published in Eur Neuropsychopharmacol 2007;17:Suppl 4.

**Mood disorders**

A symposium was dedicated to novel etiopathogenic hypotheses regarding depressive disorders. In particular, the roles of vasopressin, calcium-binding protein beta (S100B), cytokines, and glucocorticoid receptors were reviewed. Timothy Dinan (Cork University Hospital, Cork, EIRE) showed that vasopressin elicits greater adrenocorticotropic and cortisol responses in depressive patients; thus, it may represent a potential new target for antidepressant medications. S100B is a interesting glial-derived protein that functions as a neurotrophic factor. Adding to previous findings, Matthias Rothermundt (University of Münster, Münster, Germany) reported elevated central spinal fluid and serum S100B levels in patients with major depressive disorder (MDD). In depressed patients, levels of cytokines have also been found to be elevated, and Marta Kubera (Polish Academy of Sciences, Kraków, Poland) described their role in depression. Expression of proinflammatory cytokines is induced by chronic stressors and environmental insults. Cytokines lower levels of neuroprotective factors and serotonin (5-HT) by inhibiting the conversion of tryptophan, upregulating the 5-HT transporter, increasing the expression of 5-HT₁A auto-receptors and decreasing the expression of 5-HT₁B post-synaptic receptors. Finally in this session, Carmine M Pariante (King’s College London, London, UK) described the role of glucocorticoid receptors in depression, depicting them as less responsive in patients with this disorder than healthy people.

A second symposium was dedicated to treatment-resistant depression (TRD), defined as the failure to respond to at least two consecutive adequate antidepressants. In his lecture, Julien Mendlewicz (Université Libre de Bruxelles, Erasme Hospital, Bruxelles, Belgium) described the European research program on therapies for TRD, which found that ≥40% of patients enrolled had depression resistant to treatment. Possible treatment strategies were discussed. Benedikt Amann (Hospital San Boi, Barcelona, Spain) discussed new potential candidates for the treatment of bipolar disorder: tamoxifen (a protein kinase C inhibitor), chromium, omega-3 essential fatty acids, modafanil, and substances that act via inhibition of glycogen synthase-3.

**Anxiety disorders**

Presentations focused in particular on strategies for treatment-resistant patients with anxiety disorders. Borwin Bandelow (University of Göttingen, Göttingen Germany) suggested that psychological treatments should be considered for all patients with panic disorder (PD), whether they are treatment-resistant or not, given the evidence of higher efficacy of combined treatment compared with pharmacotherapy alone.

A second symposium focused on drugs that can facilitate psychotherapy. Anton van Balkom (Vrije Universiteit, Amsterdam, The Netherlands) reviewed the evidence for the efficacy of combined treatment in PD.
(Karolinska Institutet, Stockholm, Sweden) described the potential of combining psychotherapy and benzodiazepines for the treatment of resistant PD, to quickly manage anticipatory anxiety and phobic avoidance. Two other lecturers focused on the use of psychedelic substances (Ben Sessa, University of Bristol, Bristol, UK) and 3,4-methylenedioxymethylamphetamine (MDMA) (Michael Mithoefer, Private Practice Clinical Research, Mount Pleasant, SC, USA) as compounds that can facilitate the psychotherapeutic process.

Two presentations focused on neurobiological correlates of post-traumatic stress disorder (PTSD). Elizabeth Young (University of Michigan, Ann Arbor, MI, USA) presented her own study on stress response in PTSD and MDD, reporting increased cortisol levels only in those subjects who were exposed to trauma in the preceding year. Erik Vermetten (University Medical Center of Utrecht, Utrecht, The Netherlands) provided evidence of chronically increased levels of corticotropin-releasing factor and norepinephrine in patients with PTSD.

Schizophrenia

Neurological and genetic predictors of schizophrenia were presented. Eve Johnstone (Royal Edinburgh Hospital, Edinburgh, Scotland) discussed results from the Edinburgh High-Risk Study, in which healthy individuals at a high risk of schizophrenia were evaluated and followed over a period of 10 years. Gray matter loss, abnormal parietal and frontal gyrus function, and variants of the genes encoding catechol-O-methyl transferase (COMT) and neuregulin 1 have been found to be associated with the development of psychosis. Brain developmental abnormalities seem to be consistent in schizophrenia. Christos Pantelis (University of Melbourne, Melbourne, Vic, Australia) found that subjects who develop psychotic symptoms show brain contraction in the prefrontal cortex and a progressive cognitive decline in the areas of executive functions and memory. Wiepke Cahn (University Medical Centre of Utrecht, Utrecht, The Netherlands) reported progressive volume decreases in grey matter and increased lateral and third ventricles in first-episode patients. Finally, Joost Janssen (Hospital Universitario Gregorio of Madrid, Madrid, Spain) reported a loss of grey matter in the left frontal lobe observed 2 years after the first psychotic episode.

A second symposium was dedicated to treatment issues in schizophrenia. In particular, Peter Falkai (University of Göttingen, Göttingen, Germany) gave some indications when combining different antipsychotics. Clozapine has low D₁ dopamine receptor-blockade activity; thus, haloperidol or risperidone may be added to increase D₂ inhibition. Furthermore, the latter agents bind D₂ receptors for a long time, while quetiapine binds D₂ receptors for a shorter period. Therefore, combining D₂-modulating drugs with D₂/5-HT₂-modulating antipsychotics can be effective.

The hippocampus seems to be implicated in the pathophysiology of schizophrenia, as demonstrated by evidence of alterations in neuronal organization, density, and size. Paul Harrison (University of Oxford, Oxford, UK) reviewed neuropathological data supporting the impaired development of the hippocampus in schizophrenia and presented molecular studies showing the altered expression of genes involved in synaptic plasticity.

Children and adolescents

Sessions on childhood psychiatric disorders particularly focused on conduct disorders (CDs) and attention-deficit/hyperactivity disorder (ADHD). CDs and abnormal aggressive behaviors frequently occur in childhood and persist in adult life in many cases. Stephanie van Goozen (Cardiff University, Cardiff, UK) and James Blair (National Institutes of Health, Mood and Anxiety Disorders Program, Bethesda, MD, USA) described neurobiological correlates of CD, reporting reduced neuroendocrine reactivity in children and adolescents with the disorder and lower amygdala activation in children with CD with callous and unemotional traits.

Regarding ADHD, Barbara Franke (Radboud University Nijmegen Medical centre, Nijmegen, The Netherlands) reported on a genetic study on adult ADHD patients that was conducted based on the fact that vulnerability for ADHD is supposed to be strongest in forms that persist in adulthood. Dr Franke and colleagues investigated a panel of genetic polymorphisms related to dopaminergic transmission, and positive associations were obtained for the genes encoding dopamine β-hydroxylase and the dopamine transporter.

Cannabis use in adolescence being a risk factor for the development of psychosis and suicidal behavior was discussed. As stated by Maria-Paz Viveros (Universidad Complutense, Madrid, Spain), the endocannabinoid system is involved in homeostasis, particularly as regards the endocrine stress response. Thus, challenge of this system through the use of cannabis during the developmental period may alter neuroendocrine functioning and the response to stress.

In her lecture, Cecile Henquet (University of Maastricht, Maastricht, The Netherlands) reported a correlation between young age at onset of abuse and the risk of developing psychotic symptoms, and presented a replication study on the effect of the COMT gene Val158Met polymorphism in the exacerbation of psychotic symptoms.
Addiction
Drug addiction seems to result from a long-lasting neuronal reorganization in systems involved in reward-mediated learning. In his talk, Denis Hervé (University Pierre et Marie Curie, Paris, France) explained that this effect is due to an increase in dopamine transmission induced by drugs.

During detoxification, craving can be associated with an increase in opioid receptors. Tim Williams (University of Bristol) reported that alcohol- and opioid-dependent patients show higher opioid binding potential than controls. Furthermore, the level of craving was associated with binding potential.

Attention biases seem to be involved in addiction and craving. Ingmar Franken (Erasmus University of Rotterdam, Rotterdam, The Netherlands) reported that drug and alcohol abusers show enhanced processing of drug-related stimuli, and pay more attention to these stimuli. It is likely that this attention bias results from a sensitized dopaminergic system. However, cue exposure and manipulation of attentional bias, non-pharmacological treatments designed to prevent relapse, do not appear effective as changes are context specific, and thus limited to the treatment setting (Remco Havermans [University of Maastricht] and Matt Field [University of Liverpool, Liverpool, UK]).

Studies also focused on psychotherapeutic and psychosocial interventions as strategies to prevent relapse after detoxification. Falk Kiefer (University of Mannheim, Mannheim, Germany) reported evidence for the efficacy of combined psychological and pharmacological treatments.

Frank Voci (National Institute of Mental Health, Bethesda, MD, USA) reported that the efficacy of disulfiram is low if not null in cocaine dependence. Modafinil reduces the subjective response to cocaine but results are still controversial regarding its efficacy. Finally, Thomas Kosten (Baylor College of Medicine, Houston, TX, USA) described the use of antibody therapy to prevent drugs from entering the brain system. Antibodies act by antagonizing the drug, thus reducing the amount of drug in the brain. Vaccines have been investigated in preclinical studies.

Neurodegenerative disorders
A symposium was dedicated to the pathogenic mechanisms of dementia, particularly the dysmetabolism of amyloid peptides, which leads to pathological deposition upon aging. The debated pathogenic mechanism of neuritic changes as a consequence of plaque formation was supported by work on transgenic mice presented by Melanie Meyer-Lühmann (Massachusetts General Hospital, Charlestown, MA, USA) and Thomas Bayer (Saarland University, Homburg/Saar, Germany).

Tamas Revesz (University College of London, London, UK) explained how the deposition of an amyloid protein in blood vessels in the central nervous system produces different forms of cerebral amyloid angiopathies, sporadic and familiar. Interestingly, Massimo Tabaton (University of Genova, Genova, Italy) reported that aggregates of water-soluble β-amyloid appear long before amyloid deposition, representing the first form of β-amyloid accumulation, which may be useful for early detection. Finally, Takaomi Saito (RIKEN Brain Science Institute, Saitama, Japan) presented a new approach for the prevention of Alzheimer’s disease (AD) via upregulation of nephrilysin, which can degrade β-amyloid.

Psychiatric symptoms are frequent in both AD and Parkinson’s disease. As underlined by Gloria Dal Forno (Associazione Fatebenefratelli per la Ricerca, Rome, Italy), the emotional and behavioral symptoms of AD are probably the greatest source of stress for both patients and caregivers, negatively affecting their quality of life and increasing expenses related to hospitalization and institutionalization more than cognitive symptoms. In Parkinson’s disease, depression, psychotic symptoms, and cognitive impairment are frequent. Depression, occurring in 40% of patients, can be a consequence of decreased serotonergic or noradrenergic tone and dopamine deficiency, as stated by Regina Katzenschlager (Sozialmedizinisches Zentrum Ost von Vienna, Vienna, Austria). Treatment with antidepressants can be useful, particularly nortriptylin, but also selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase B inhibitors.

The lifetime prevalence of hallucinations in Parkinson’s disease is 50%. As described by Gilles Fenelon (Hôpital Henri Mondor of Creteil, Creteil, France), hallucinations involve all sensory modalities, and complex visual hallucinations are the most common. Disease-related factors may be the basis of psychosis, but the use of dopaminergic treatments can also be related to psychotic symptoms. Different forms of cognitive impairment can be observed in patients with Parkinson’s disease. Heterogeneity indicates deficits in different brain areas, such as the fronto-subcortical, cortical, or hippocampal area, as described by Carmen Janvin (University Hospital of Stavanger, Stavanger, Norway).

Cardiovascular diseases and psychiatry
Cerebrovascular stroke is the event that most commonly causes neuropsychological impairment. Martine van Zandvoort (University of Utrecht, Utrecht, The Netherlands) described neuropsychological deficits associated with vascular brain disease. Cognitive and emotional outcome seems to depend on focal damage, diffuse neuronal dysfunctions, and patient variables such as age, gender, and comorbidities. Robert Baldwin (University of Manchester, Manchester, UK) described how ischemic disease is associated with a greater incidence of new depression and a
poorer outcome in patients suffering from depression prior to the ischemic event. MDD complicates cardiovascular disorders and is associated with a three-fold increase in mortality, independently of the medical condition. Alexander Glassman (Columbia University, New York, NY, USA) presented evidence for the efficacy of cognitive behavioral therapy and SSRIs in this setting.

Cardiovascular disease is particularly frequent in MDD. Thomas Baghai (University of Munich, Munich, Germany) and colleagues investigated a gene associated with cardiovascular disease, namely that encoding angiotensin I-converting enzyme, in depressed patients and found a variant within this gene that is significantly associated with MDD and hyperactivity of the hypothalamic-pituitary-adrenal axis. Thus, a genetic association between depression and cardiovascular disease was hypothesized. Finally, impaired baroflex sensitivity has been found in many patients affected by psychiatric disorders. Caroline Sevoz-Couche (Faculté de Médecine Pierre et Marie Curie, Paris, France) found that activation of 5-HT3 receptors inhibits bradycardic responses. Thus, these receptors may represent a relevant target for reducing cardiac complications in patients with psychiatric disorders.

**New molecules in psychiatric disorders**

**Nitric oxide**

Nitric oxide (NO) is the first member of a new class of neurotransmitter, the gaseous diffusible messengers. Ömer Akyol (Hacettepe University of Ankara, Ankara, Turkey) described how NO can interact with other neuromodulators to alter their effects on neurotransmission. NO can also interact with proteins, particularly with cytochromes, which are membrane-bound proteins, impairing oxidative phosphorylation. NO reacts with molecular oxygen to form peroxynitrite, which is harmful to cellular structures and is associated with many processes that cause cellular injury. Thus, NO can play an important role in neurodegenerative disorders. Daniel Klamer (University of Göteborg, Göteborg, Sweden) reported that NO synthase inhibitors ameliorate cognitive impairments induced by schizophrenomimetic drugs (e.g. phencyclidine) in rats.

Andreas Reif (University of Würzburg, Würzburg, Germany) described a genetic study on a gene coding for NO (NOS1) in different psychiatric samples. He found positive associations between the gene and schizophrenia, Cluster B personality disorders, adult ADHD, and criminality. Thus, NOS1 may be involved in disruptive behaviors.

Several preclinical studies suggested a role for NO in affective disorders. Gregers Wegener (University of Aarhus, Risskov, Denmark) described how NO regulates many conventional neurotransmitters and how antidepressants modulate levels of NO in the hippocampus. Thus, NO is a potential target for antidepressant and anxiolytic treatments.

**Galanin**

Galanin is a recently discovered neurotransmitter. Tomas Hökfelt (Karolinska Institutet) described the galanin system. To date, three galanin receptors (GalRs) have been discovered and found to be widely distributed in the brain. Studies have shown that galanin has neurotrophic effects and inhibits both noradrenergic and serotonergic systems. David Wynick (University of Bristol) explained how galanin has been shown to have neurotrophic properties in models of excitotoxic damage and multiple sclerosis. These trophic effects seem to be mediated by GalR2. Elliot Mufson (Rush University Medical Center, Chicago, IL, USA) found that basal forebrain neurons survive in the presence of amyloid if hyperinnervated by galanin-containing fibers. Results of studies on galanin and non-galanin innervated cells in patients with AD and controls confirmed the neuroprotective effects exerted by galanin.

On the other hand, studies have shown that administration of galanin to the brain impaired performance in various learning and memory tasks in mice. John Robinson (University of Stony Brook, Stony Brook, NY, USA) described more recent evidence that galanin antagonists have cognitive-enhancing effects, although the mechanisms by which galanin is involved in memory and learning have yet to be elucidated.

Galanin inhibits both noradrenergic and serotonergic systems, and Sven Ögren (Karolinska Institutet) described how genetic and pharmacological studies suggest a role for this neuropeptide in depression-like behaviors in animals. Antidepressant effects may be obtained by antagonizing GalR1 and GalR3, or by stimulating GalR2.

**Kynurenic acid**

Kynurenic acid (KYNA) is a product of the normal metabolism of the amino acid l-tryptophan. Increases in KYNA levels are mediated by the enzyme indoleamine 2,3-dioxygenase (IDO), which initiates the conversion of tryptophan acid to KYNA. Dietmar Fuchs (Biocenter Innsbruck Medical University, Innsbruck, Austria) described how IDO can be induced by proinflammatory cytokines. Thus, cellular immune activation, which occurs in response to disease but also with aging, is associated with increased tryptophan degradation by this enzyme. Since tryptophan is the precursor of serotonin, cytokine-induced degradation may be of importance in the pathogenesis of depression, cognitive impairment, and neurodegenerative disorders such as Alzheimer’s, Parkinson’s, and Huntington’s disease, and vascular dementia.
It has been shown that KYNA can be neuroactive. KYNA may regulate glutamatergic and dopaminergic transmission. Indeed, Robert Schwarcz (University of Maryland, Baltimore, MD, USA) found that focal infusion of KYNA reduced basal extracellular levels of glutamate and dopamine in the neostriatum and prefrontal cortex – brain areas that are involved in schizophrenia. Sophie Erhardt (Karolinska Institutet) reported that pharmacologically elevated levels of KYNA increase the activity of midbrain dopaminergic neurons. The finding of elevated levels of KYNA in the cerebrospinal fluid was replicated by her group of investigators in a large sample of drug-naïve schizophrenia patients. Furthermore, a relationship between KYNA concentration and the response of midbrain dopaminergic neurons to clozapine was reported.

KYNA increases responsiveness to methamphetamine in pharmacologically treated rats. Yasushi Kajii (Mitsubishi Pharma Corporation, Kanagawa, Japan) reported that in these rats treatment with haloperidol reduces behavioral sensitization and alters gene expression, which can be predicted to reduce KYNA production. He suggested that decreased KYNA levels may potentially attenuate the recurrence of psychosis.

In conclusion, a number of novel and pioneering data are emerging from current research on neuropsychiatric disorders: new etiopathogenic hypotheses, new compounds as potential therapies, and new discoveries with regard to neurological constituents and functioning. These achievements are promising and further sustain the extension of scientific research in neuropsychology in order to better understand, prevent, and treat neuropsychiatric disorders.

Disclosures
The authors have no relevant financial relationships to disclose.
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