Depression: Beating the odds for remission

Depression takes a huge toll on society in lost productivity, family distress and dysfunction, and suicide, explained John H. Greist (Healthcare Technology Systems, Inc, Madison, WI, USA).

Depression is a multidimensional illness, reported more often in women than in men, with a host of emotional, physical and associated symptoms. “The cardinal emotional symptoms are sadness, lack of energy, lack of interest, feelings of guilt, and suicidality,” Dr. Greist told the audience.

Treatment phases of depression can include response, remission, recovery, relapse and recurrence. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study provides some real-world insights into outcomes in patients with depression treated with initial therapy, switching to a different drug and augmentation strategies. This study included 2,876 outpatients with major depressive disorder (MDD) seen in 23 psychiatric and 18 primary care ‘real-world’ settings who were initially treated with flexible doses of citalopram for up to 14 weeks [1]. Approximately one third achieved remission on monotherapy with citalopram, switching from citalopram to a different antidepressant achieved remission in 20% to 25%, and augmentation of citalopram with either buspirone or sustained-release bupropion achieved remission in 30% [2,3].

Remission may not be long-lasting due to delayed onset of remission, unresolved symptoms of depression, recurrent episodes of depression and systemic issues, Dr. Greist explained. Delayed onset of remission is associated with poor outcome [4], he continued. Also, some patients respond but do not achieve remission. Residual symptoms of depression predict worse outcomes [5], he added.

Making an accurate diagnosis and getting the patient on the right treatment increases the chances of response, recovery and remission. In clinical practice, many patients are undertreated and do not have...
**MAJOR DEPRESSIVE DISORDER A HUGE BURDEN TO SOCIETY**

MDD takes a huge toll on patients’ ability to work, function, and perform daily activities, according to a large survey from the U.S. and European Union (EU). Julie C. Locklear (AstraZeneca Pharmaceuticals, LP, Wilmington, DE, USA) presented survey results on the burden of depressive illness at a poster session.

Worldwide, the six-month prevalence of MDD ranges from 3.8% to 9.9%. The survey included 474 physicians from the U.S. and five European countries recording information on 1,582 patients with MDD and 8,459 subjects classified as “All Other Neuroses” (AON). Of patients treated for MDD about 65% was female and mean age was 47 years.

In both the EU and US, patients with MDD had a higher mean number of symptoms than those with AON (17.7 vs. 9.2 in the EU, respectively, p < 0.001) and 15.9 vs. 7.7, respectively, in the U.S., p < 0.001). Most patients with MDD reported between 11 and 15 symptoms, whereas most patients with AON reported between 6 and 10 symptoms. In the EU, 25% of the MDD patients suffered more than 20 symptoms vs. 23% in the U.S., whereas only 6% of EU patients and 3% of U.S. patients with AON reported having more than 20 symptoms.

When patients were asked how much impact on their lifestyle these symptoms had, (ranging from 1 [not affected] to 10 [not able to continue with normal activities at all]), the average score for patients with MDD was 6.3 compared with 5.0 in the EU and 4.5 in the U.S for those with AON.

**Reference:**


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**Depression with psychiatric comorbidity; recognition and management**

Psychiatric comorbidity commonly occurs in patients with depression but is often not recognised, said James W. Jefferson (Department of Psychiatry, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA). Common psychiatric comorbidities include general anxiety disorder as well as specific phobias, panic disorder, post-traumatic stress disorder, seasonal affective disorder, obsessive-compulsive disorder, personality disorder and substance use disorder (drugs and/or alcohol).

It is easy to miss psychiatric comorbidity in patients with MDD in clinical practice, partly as a result of time constraints. “You won’t find something unless you spend a lot of time trying to find it,” Dr. Jefferson said. “It takes about 1 hour and 43 minutes to administer the Structured Clinical Interview for DSM-IV (SCID) and another 45 minutes to check a patient’s medical records. Most psychiatrists in the U.S. don’t have the time to do that.” Another problem with the U.S. healthcare system is that many patients with MDD never see a psychiatrist or other doctor.

Tools for diagnosing comorbid psychiatric conditions include SCID, the Mini-International Neuropsychiatric Interview (MINI), the Primary Care Evaluation of Mental Disorders (PRIME-MD), the Mental Health Screener and the Psychiatric Diagnostic Screening Questionnaire (PDSQ). Dr. Jefferson said that the MINI and PDSQ are the ones most commonly used. The STAR*D study had findings that are generalisable to the real world; it found a substantial amount of comorbidity in patients with depression who were recruited from community practices [1]. At baseline, the PDSQ was used to assess comorbidity in this group of patients; only one third of subjects had no psychiatric comorbidity, 65.2% had one or more comorbidities, and 12.9% had four comorbidities (Figures 1, 2).
PREDICTORS OF SUICIDAL IDEATION IN POST-PARTUM WOMEN WITH NEURO-Psychiatric Illness

Post-partum suicide is a leading cause of mortality. According to a prospective observational study of perinatal psychiatric illness, risk factors for post-partum suicidal ideation were distinct from those for suicidal ideation unrelated to childbirth and the post-partum period, although there is some overlap. Strongest predictors of risk of suicidal ideation were current major depressive episode and history of substance abuse. Histories of eating disorder and of miscarriage were also strong predictors. Lead author was Tamara E. Weiss (Emory University, Atlanta, GA, USA).

Four hundred women with psychiatric illness were enrolled in the study either during pregnancy or prior to conception; mean age was 24 years; 91.5% were Caucasian, and 86.8% were married. Suicidal ideation was present in 9.75% of the women as measured on the Beck Depression Inventory and in 7.75% on the Hamilton Rating Scale for Depression (HRSD). About 60% had both Mood and Anxiety Disorder and 36.5% had both Mood and Substance Abuse Disorder.

Multivariate logistic regression analysis showed that a current major depressive episode had an odds ratio (OR) of 10.77, and a 95% confidence interval (CI) of 2.64–44.01 for predicting suicide ideation. For other significant predictors, OR were as follows:

- History of opioid abuse or dependence, OR 29.63, 95% CI 1.66–528.58;
- History of polydrug dependence, OR 64.35, 95% CI >999;
- History of eating disorder, OR 6.47, 95% CI 1.74–24.05;
- History of miscarriage, OR 7.49, 95% CI 1.62–34.55.

Surprisingly, psychiatric disorders and lifetime mood disorders were not strong predictors of suicidal ideation in this sample.

Reference:

A greater number of Axis I comorbid disorders were found in patients with younger onset of MDD, longer duration of MDD, greater severity of MDD, poorer quality of life, more impaired daily function, more prior suicide attempts, and in those treated in primary-care practices. Dr. Jefferson noted that “the presence of comorbid medical or psychiatric disorders may be associated with or induce biological changes that render otherwise useful treatments ineffective.”

Although comorbid psychiatric illness is best treated within an integrated mental-health system that provides comprehensive care and case management, even when such programs exist, patients with MDD and other psychiatric disorders are not always willing to participate in them.

The choice between available SSRIs is not always clear, he continued. Some SSRIs are only approved for one or two indications (e.g., citalopram, fluvoxamine and duloxetine), “but just because an antidepressant isn’t indicated for a comorbid psychiatric indication doesn’t mean it doesn’t work,” he said. Some SSRIs have as many as seven indications (e.g., paroxetine). There are no studies to guide treatment selection for depression with psychiatric comorbidity. The approach is basically empirical, trying to match the antidepressant of choice with the existing comorbidity on the basis of FDA approval, but this is not always effective, he said.

Cognitive behavioural therapy (CBT) has been found effective for MDD and comorbid anxiety disorders and can be combined with drug treatment, but CBT is not widely available.

For the present, Dr. Jefferson advised psychiatrists to get ready (evaluate), aim (diagnose) and fire (treat). He emphasised that more effectiveness research on MDD and psychiatric comorbidity is greatly needed.
DEEP BRAIN STIMULATION FOR TREATMENT-RESISTANT DEPRESSION

In 2005, Mayberg et al. reported encouraging results with deep brain stimulation (DBS) to the subgenual cingulate cortex in a pilot study of a small number of patients with treatment-resistant MDD. These findings have been replicated in a larger series of patients in a multicentre trial reported at a poster session by Sidney H. Kennedy (University Health Network, Toronto, ON, Canada).

The study included 20 patients with MDD and a current depressive episode at least 24 months long who were treatment-resistant (i.e., failed at least four depression treatments including Cognitive Behavioural Therapy). All patients had a Hamilton Depression Rating Scale for Depression (HRSD-17) of 20 or higher.

Five of the cases were treated in Vancouver, six in Montreal, and nine in Toronto. At the time the poster was prepared, the six-month evaluation was completed on 16 patients, nine (56%) of whom had at least a 40% improvement on HRSD. After the poster was prepared, six additional patients reached the six-month mark, and now 15 of 19 patients have had at least a 40% improvement on the HRSD, for a response rate of 79%.

There is tremendous interest in DBS, and these are robust findings, said Prof. Kennedy. The technique entails inserting electrodes into the subgenual cingulate cortex Brodmann Area 25, which is thought to be disregulated in brains of depressed patients. Only about 50 cases of MDD worldwide have been treated with DBS, all of them highly refractory to other treatments. Prof. Kennedy said that these results warrant a double-blind randomised trial of the technique.

Reference:

Moar than the blues: medical comorbidity in perinatal depression

The lifetime risk of depression is twice as high for women as for men, explained Maria Muzik (Department of Psychiatry, University of Michigan, Ann Arbor, MI, USA). Life transitions, such as adolescence, premenstrual, peripartum and perimenopause, make women more vulnerable to depression and this vulnerability appears to be related to hormonal fluctuations during these transitions. Dr. Muzik’s presentation focused on depression during pregnancy and the post-partum period.

“We used to think that pregnancy prevented depression because of increases in oestrogen, but now we know that is not the case. The percentage of women who experience depression during pregnancy is 14% [9] and about 10–15% of women experience post-partum depression [10],” she told listeners. “The percentages are similar even in cultures where women have lots of support from extended family members,” she added.

Post-partum ‘blues’ are distinct from depression and are much more common; “the blues are almost the norm,” she said. Anywhere from 50% to 85% of women report feeling ‘blue’ or sad after giving birth. Psychosis is rare, she said, occurring in one or two women per 1,000 [11].

Perinatal depression, according to DSM-IV-TR criteria for major depression, has onset within the first four weeks of giving birth. Dr. Muzik said that in her experience, most post-partum depressions have onset from 6 to 12 weeks [10]. Unique features of post-partum depression include prominent anxiety related to loss of control, loneliness, and intrusive and obsessive thoughts of harming the baby.

Post-partum psychosis has a more rapid progression, within a week or two, and requires immediate treatment. Sometimes this represents new onset of bipolar disorder. By contrast, post-partum ‘blues’ typically begins two to four days after giving birth and usually resolves by the second week. The ‘blues’ are characterised by labile mood, tearfulness and mild sleep disturbances. No treatment is required, unless the episode is prolonged and other symptoms develop, such as suicidality.

Several user-friendly instruments can screen women for perinatal depression: Edinburgh Postnatal Depression Scale (EPDS, 10 items); Beck Depression Inventory (BDI-II, 21 items); and Postpartum Depression Screening Scale (PDSS, 35 items). The EPDS is the oldest and most common one and requires only a few minutes to score [12]. A score of 12 (range 0–30) has good sensitivity/specificity for MDD, she said, and a score of nine signals probable mild depression.

“Screening alone is not enough. These women require treatment,” she said. It is important to let the obstetric provider know when an EPDS score signals the presence of depression, so that he/she can discuss depression and treatment with the patient. Often patients at risk for depression fall through the gap and are not treated or followed appropriately. A collaborative-care model is needed to standardise follow-up, provide support and education, provide referrals for treatment, and cooperate with specialty care.

Untreated perinatal depression has adverse physical and emotional consequences for mother and child. Maternal depression increases the risk of ectopic pregnancy, miscarriage, hyperemesis, preterm contractions and pre-eclampsia [13,14]. After children of mothers with depression are born, they are at risk for poor follow-up and routine care and the mother’s misuse of pediatric emergency services, she said.

A cohort of children whose mothers were depressed and anxious during pregnancy had significantly greater psychiatric problems at 81 months compared with the general population (Figure 3) [15]. Furthermore, these effects were seen at age 4 and persisted until 81 months.
Subclinical hypothyroidism can masquerade as perinatal depression, with symptoms of fatigue, depression, weight gain, impaired memory and concentration, and muscle pains. It is important to diagnose subclinical hypothyroidism in pregnant women, because it can progress to clinical hypothyroidism and adverse health consequences for both mother and child. Subclinical hypothyroidism is defined as thyroid stimulating hormone (TSH) > 4.12 mIU/L in the presence of normal T3/T4 level. Women with a history of thyroidism or difficulty conceiving should be screened for thyroidism before conception.

Treatment of maternal depression during pregnancy is problematic, due to concerns about teratogenicity of antidepressants. Mild to moderate depression can be treated with psychotherapy, but severe depression will require pharmacotherapy, Dr. Musik said. The FDA has classified the following antidepressants as having no evidence of human risk: buspirone, the tricyclic antidepressants and SSRIs (except paroxetine).

The rule for treating depression during pregnancy is to balance the risk of a recurrent episode with the risk of medications. Avoid polypharmacy and use the lowest effective dose of medications with the lowest teratogenic effects, she suggested. The risk of teratogenicity is highest during the first trimester of pregnancy; patients on an antidepressant should take 3 to 5 mg folic acid daily.

Studies are inconsistent regarding antidepressants and breast feeding. Most medical associations encourage breastfeeding for the first 6 to 12 months of life, yet all medications are transferred to breast milk, albeit at low concentrations. Dr. Musik concluded that the use of pharmacotherapy in peripartum asks for a case-by-case decision. The risk of untreated maternal depression has to be balanced with the risks of foetal exposure.

**Depression, physical symptoms and pain: a roadmap for psychiatrists**

Physical comorbidities are the norm for patients with depression and contribute to the huge burden and costs of MDD, said John F. Greden (Department of Psychiatry, University of Michigan, Ann Arbor, MI, USA). Treatment of comorbid pain and physical symptoms is based on an understanding of pain mechanisms and should be guided by a ‘road map,’ he said (Figure 4).

Shared symptoms of depression and physical illness can include headache, dizziness, joint pains, back pain, fatigue, weakness, abdominal pains and muscle and chest pains. Pain is typically the chief presenting complaint of patients who consult physicians. The more physical symptoms and the more sites for pain a patient has, the more likely the diagnosis

**DEPRESSION AND ALCOHOL ABUSE CLOSELY LINKED IN WOMEN, NOT MEN**

Depressive symptoms correlated with alcohol craving in women, but not in men, according to a large retrospective clinical data set of more than 300 patients voluntarily participating in a 28-day intensive addiction program at the Mayo Clinic in Rochester, MN, USA. Women appeared to be drinking to relieve feelings of anxiety and depression, whereas men may be drinking just to feel good, speculated lead author Nelli Boykoff (Mayo Clinic, Rochester, MN, USA).

On admission to the program, women had significantly higher scores for depressive symptoms (p = 0.001) and alcohol craving (p = 0.0001) compared with men. The gender difference persisted in those with a clinical diagnosis of alcohol dependence only (n = 92) or a dual diagnosis (n = 139; alcohol dependence plus depression, bipolar disorder or anxiety disorder).

The retrospective analysis included 364 patients (135 women and 229 men). Mean age was about 48 years and subjects began drinking at about age 20. All were heavy drinkers; women averaged 10.8 drinks per day and mean, 13.8 drinks per day. Fifty-three per cent were daily drinkers; 75% fulfilled the National Institute of Alcohol Abuse and Alcoholism (NIAA) definition of hazardous users (>5 drinks/day for men and >4 drinks/day for women).

A correlation between depression and alcohol craving scores in women (not men) was seen in those with alcohol dependence alone (r = 0.78, p < 0.0001) and in women with dual diagnosis (r = 0.36, p = 0.01).

This is one of the first studies to show gender differences regarding clinical correlates of alcoholism. Further study may reveal gender-specific targets for treatment of alcohol craving.

## TANGLED UP IN BLUE

### STEREOTYPED RESPONDING IN MAJOR DEPRESSION

A small, preliminary study suggests that patients with MDD exhibit more stereotyped repetitive behaviour and substantially slower performance on psychomotor tasks than healthy volunteers. These phenomena, which have also been identified in patients with schizophrenia, appear to be correlated in MDD. Didier Schrijvers (University of Antwerp, Antwerp, Belgium) was lead author of this poster presentation at APA.

The study included 20 patients with MDD and 20 healthy volunteers. Mean age of patients was 38.8 years; eight were males. All had a unipolar Major Depression episode and Hamilton Depression Rating Scores of 18 or above. Patients with comorbid psychiatric disorders were excluded. Nineteen patients were taking antidepressants and four of them were treated with augmentation strategies (low-dose neuroleptic or benzodiazepine). Healthy controls had a mean age of 37.4 years; six were males. Subjects were tested with the Stereotypy Test Apparatus (STA) and asked to copy single lines, simple figures and complex figures as fast as possible. STA scores (redundancy of two consecutive presses of computer buttons) were significantly higher in patients versus controls (p < 0.05). Psychomotor responses (reaction time and movement time) were significantly slower in patients versus controls for all three tasks: single-line reaction time and single-line motor time (p = 0.01 for both); simple-figure reaction time and motor time (p = 0.01 for both); complex-figure motor time (p < 0.001).

These results suggest that patients with MDD may have impaired executive function. Further studies in medication-free depressed subjects are needed to confirm these findings.

**Reference:**

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### RECOMMENDED APPROACH (‘PRE-TRIP ROADMAP’)

![Recommended Approach (Pre-Trip Roadmap)](image)

1. Screen (PHQ-9 and Pain Scale) and tell patient you will monitor
2. Identify and refer for treatment of 'peripheral' pain
3. Educate BEFORE treatment starts about length of treatment, healthy sleep, avoidance of alcohol and OTC medications, exercise, etc.
4. Start CBT
5. Start SNRIs or tricyclics at low dose and increase slowly
6. Begin exercise programme after 1 week; start low, go slow
7. If inadequate improvement, consider pregabalin or gabapentin after 6–8 weeks if necessary (higher dose at night)
8. If necessary after 6–8 weeks, add tramadol in low doses
9. Zolpidem or trazodone for sleep; avoid overuse or routine use of BZDs
10. Begin discontinuation of some medications before adding more medicines
11. Long treatment periods are indicated (several months); be persistent
12. Consider cytochrome P450 genetic polymorphism if patient ‘unable to tolerate’ multiple medications
13. Passionately promote continuation of CBT, exercise, healthy sleep, nutrition
14. Continue maintenance treatment once the person is improved

PHQ-9 = Patient Health Questionnaire; OTC = over the counter; SNRI = selective norepinephrine reuptake inhibitor; CBT = cognitive behavioural therapy; BZD = benzodiazepine

**Source:** Greden JF. Data presented at the 2008 Annual Meeting of the American Psychiatric Association (APA). Washington, DC, USA, 2008.
Support for symptom improvement with dual SSRI and SNRI inhibition

Symptoms of depression, as well as somatic symptoms (i.e., disturbances in sleep, and appetite and gastrointestinal problems), were improved in patients with MDD treated with duloxetine, according to a post-hoc analysis of a double-blind, parallel design trial reported by Susan G Kornstein (Virginia Commonwealth University Mood Disorders Institute, Richmond, VA, USA).

The analysis was designed to assess differences in symptom improvement and tolerability between males and females with MDD treated with duloxetine. Patients (n = 652) were randomised to receive one of three duloxetine doses: 30 mg per day, 30 mg twice a day or 60 mg per day. After the first week of treatment, all patients received 60 mg per day for an additional five weeks. The analysis presented at APA pooled all dose groups and stratified patients according to gender. Symptoms were evaluated using the Association for Methodology and Documentation in Psychiatry adverse event scale (AMDp) and the 17-item Hamilton Depression Rating Scale (HAMD-17).

Baseline HAMD-17 total scores were almost similar between males (21.1) and females (21.7). At baseline, no significant differences were observed between genders for HAMD-17 factors, except more psychomotor retardation was seen in females. AMDP symptom category scales were also similar at baseline between genders, except more appetite disturbance was seen in females. Mild to moderate sleep disturbances were reported in both genders at baseline, according to mean AMDP scores; other symptom categories were mild at baseline.

At six weeks, duloxetine reduced HAMD-17 scores by about 11 points in both genders and no statistically significant differences according to gender were found for total HAMD-17 score, the Maier subscale or other HAMD-17 factors.

From baseline to end point, duloxetine improved sleep disturbances, appetite disturbances and gastrointestinal disturbances to a similar extent in both genders. Other somatic disturbances (headache, heaviness in legs, hot flashes, chills and conversion symptoms) were similarly improved from baseline in males and females. A significant difference from baseline to end point was seen for decreased appetite for males (0.28 vs. 0.17 point improvement for males vs. females, p = 0.05). Micturition difficulty worsened in males and improved in females from baseline to end point (p < 0.001) and backache improved in males versus females (p = 0.004).

References


TANGLED UP IN BLUE

PREVALENCE OF SUBSTANCE DEPENDENCE, PSYCHIATRIC DISORDERS AND CHRONIC MEDICAL CONDITIONS IN A DETOXIFICATION/REHABILITATION SETTING

Substance-related disorders and psychiatric/medical conditions have a high rate of co-occurrence, according to analysis of a large database of electronic medical records of 5,588 patients discharged from inpatient detoxification and rehabilitation programs from October 1, 2005, through September 30, 2006. These findings confirm the high rates of comorbidity of substance dependence and psychiatric and medical illness reported in large epidemiologic studies. Lead author of the study, presented at a poster session, was William Meehan (AdCare Hospital, Boston, MA, USA).

Median age was 43 years; 70% were male and 85% were Caucasian. The most prevalent substance abuse diagnoses were for: opioids (47%), alcohol (44%), cocaine (25%) and sedative-hypnotic-anxiolytics (21%). Overall, 4,655 patients (83%) had at least one Axis I psychiatric disorder (mood, anxiety, or psychosis), and 3,552 patients (64%) had at least one chronic medical condition (hypertension, hepatitis C, chronic pulmonary condition, hypercholesterolaemia, diabetes, alcohol-related liver condition, pancreatitis, HIV or AIDS). The majority of patients (54%) had both psychiatric and medical disorders; 29% had psychiatric disorders only and 9% had medical conditions only. Only 8% had no co-occurring disorders.

These findings underscore the importance of designing integrated collaborative treatments for patients with substance-related and comorbid psychiatric/medical disorders. A collaborative model includes a team of experts in internal medicine, addiction medicine, nurses, counsellors and mental health professionals.

Reference:

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