ANTICYTOKINE TREATMENT FOR DEPRESSION?

One mechanism by which the immune system communicates with the brain might be via inflammatory cytokines, which have been implicated in the pathophysiology of depression. Depressed patients appear to have elevated levels of circulating inflammatory cytokines, which may precede clinical symptoms. Patients with hepatitis C often are treated with interferon, which induces cytokines, and up to 25% of those treated become depressed. And resistance to antidepressant drugs has been blamed on inflammatory system activation, which raises a potential therapeutic target.

How best to combat inflammation? Nonsteroidal anti-inflammatory drugs (NSAIDs) appear to have antidepressant effects, but these agents possess many other properties, such as effects on glucocorticoid receptors, which could have an impact on depression through mechanisms beyond inflammation.

Cytokine modulators, by contrast, target specific cytokine pathways and are more purely anti-inflammatory. Examples are the immunosuppressants adalimumab (Humira), etanercept (Enbrel), infliximab (Remicade), and tocilizumab (Actemra), which are prescribed to treat chronic inflammatory conditions such as arthritis, plaque psoriasis, ankylosing spondylitis, Crohn disease, and ulcerative colitis. In addition to tracking clinical benefits for the primary disease, many clinical trials of these compounds for such disorders report secondary outcomes, including changes in depressive symptoms. Kappelmann et al conducted a systematic review and meta-analysis of secondary data from clinical trials of anticytokine treatment in chronic inflammatory conditions to assess effects on depression.

The authors identified seven randomized controlled trials with 2370 participants, which compared anticytokine treatment with placebo. They found a significant antidepressant effect of anticytokine medications. Most commonly studied were anti-tumor necrosis factor drugs. Looked at individually, adalimumab, etanercept, infliximab, and tocilizumab all produced statistically significant benefits against depressive symptoms compared with placebo.

For the time being, the idea that anticytokine therapy might be an avenue to treat depression must be considered preliminary. But the concept of a role for inflammation in the etiology of depression and as a potential therapeutic target is supported by a growing body of evidence and surely warrants additional study. Dr Kappelmann’s group calls for randomized controlled trials of cytokine modulators specifically to combat depression.


ANTIDEPRESSANTS AND FETAL MALFORMATIONS

Roughly half of pregnancies are unplanned, and many women are well into their first trimester before they know they are pregnant. Depression is common in women of childbearing age, and thus many women take serotonergic antidepressants during the first trimester of pregnancy, a time of rapid fetal organ development. With government funding, Bérard and others in Canada conducted a register-based cohort study of depressed pregnant women to determine the association between antidepressant exposure and the risk of major congenital malformations in offspring.

Using data from the Quebec Pregnancy Cohort, investigators identified women who had given birth to a live baby and either had a diagnosis of depression or anxiety while they were pregnant or had taken an antidepressant in the year before becoming pregnant. To control for confounding by indication and lifestyle factors, such as smoking and alcohol use, data from the cohort of antidepressant-treated women were compared with data from pregnant women with the same diagnoses who were not treated with medication.

The entire sample comprised 18,487 pregnant women. When individual antidepressants were evaluated, only citalopram (Celexa and others) was significantly associated with an overall
increased risk of major congenital malformations, although the most frequently prescribed antidepressants showed a statistical trend in the same direction. Antidepressants that inhibit the reuptake of serotonin (selective serotonin reuptake inhibitors [SSRIs], serotonin-norepinephrine reuptake inhibitors [SNRIs], and amitriptyline [Elavil and others]) significantly increased the risk of specific organ defects. For example,
- the SSRI paroxetine (Paxil and others) increased the risk of cardiac and ventricular/atrial septal defects;
- the SSRI citalopram increased the risk of musculoskeletal defects and craniosynostosis;
- tricyclic antidepressants (mostly amitriptyline) increased the risk of eye, ear, face, neck, and digestive defects; and
- the SNRI venlafaxine (Effexor and others) increased the risk of respiratory defects.

Serotonin plays a vital role in healthy fetal development. Serotonergic antidepressants cross the placental barrier and block serotonin reuptake transporter sites, which impairs normal serotonin flow and function. Animal experiments suggest that drugs that alter serotonin reuptake can affect morphogenesis and organogenesis, which supports the findings of this study.1

But the overall increase in risk to the fetus from antidepressant exposure during pregnancy is relatively low. And the risks to mother and offspring of untreated depression and anxiety can be higher and potentially more severe. The safety of mother and baby is always a paramount concern. Ideally, any woman of childbearing potential should be advised about the risks to her and a future baby of treating versus not treating a psychiatric condition. If a woman with depression or anxiety is pregnant, first consideration should be given to treatment strategies with the lowest risks, including evidence-based psychotherapies.


**SLEEP MEDICATION IN DEPRESSED ADOLESCENTS**

Current strategies to treat depression in adolescents are no more successful than those for adult patients. Among adolescents with major depressive disorder (MDD), 40% or more fail to respond adequately to an initial intervention, and complete remission is only achieved in about one-third.1 Residual symptoms of depression are associated with a higher risk of relapse. The most common residual symptom after acute treatment for adolescent depression is sleep disturbance.1

Trazodone (Desyrel and others) is the drug most often prescribed to treat sleep disturbance in adolescents with mood and anxiety disorders.1 Data from the Treatment of Resistant Depression in Adolescents (TORDIA) study suggest that this approach may be counterproductive.1

In the TORDIA trial, adolescent patients with MDD who failed to respond to treatment with a selective serotonin reuptake inhibitor (SSRI) were randomly assigned to switch to one of the following: (1) a different SSRI; (2) extended-release venlafaxine (Effexor XR and others); (3) a new SSRI plus cognitive-behavior therapy (CBT); or (4) venlafaxine plus CBT.2 There was no difference in response to different antidepressants, but the addition of CBT to medication was associated with a 12-week response rate of 54.8% versus only 40.5% in subjects who received medication alone.

Of particular note, patients who received protocol-permitted sleep medications showed a significantly lower response rate than patients who did not: 32.7% versus 50.7%.2 In a follow-up analysis to their research, the TORDIA investigators examined whether this observation applied equally across all classes of sleep medication and treatment.3

Depressed adolescents who received adjunctive trazodone for sleep were six times less likely to have a positive depression response than patients who took no sleep medication (P = .001). They were also three times more likely to exhibit self-harm (P = .03). These striking differences persisted even after researchers adjusted for baseline differences associated with trazodone use. Of 13 patients treated with trazodone in addition to the SSRIs paroxetine (Paxil and others) or fluoxetine (Prozac and others), none responded. By contrast, in subjects who took other sleep medications, there was no difference in depression treatment response compared with subjects who took no sleep medications.

Shamseddine and associates caution that sleep medication in their TORDIA study was prescribed by clinician discretion—not randomly per protocol.1 Conceivably, therefore, there could be biases that account for their striking findings. Nonetheless, the authors suggest reconsidering the use of trazodone to facilitate sleep in depressed adolescents.

If future research confirms this finding of a negative effect of coadministered trazodone in depression treatment, what could explain it? Trazodone is metabolized to m-chlorophenylpiperazine (mCPP), which in turn is metabolized by cytochrome P450 (CYP) 2D6 and excreted.
Fluoxetine and paroxetine are potent inhibitors of CYP 2D6. Their coadministration with trazodone could, therefore, lead to high levels of mCPP, which have been associated with anxiety, dysphoria, and agitation.¹ Conceivably, this pharmacokinetic interaction could explain the poor antidepressant response in patients treated with trazodone plus one of these SSRIs, as well as the increased incidence of self-harm.

These provocative findings call for additional study. In the meantime, clinicians treating depressed adolescents should carefully weigh the choice of an intervention for sleep disturbance, and especially consider nonpharmacologic approaches.


²Brent D, Emslie G, Clarke G, et al. Switching to another SSRI or to venlafaxine with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression: The TORDIA randomized controlled trial. JAMA 2008;299:901-913.

LITHIUM IN DRINKING WATER: EFFECTS ON ADOLESCENTS

Lithium is a natural trace element, often dissolved in groundwater and found in varying quantities in drinking water. For more than half a century, lithium has been prescribed as a mood stabilizer, and it also has antisuicidal effects. Ecological studies have come to divergent conclusions about the association between lithium content in drinking water and regional rates of suicide and violent crimes.¹ With foundation and government support, Ando and colleagues studied the relationship between lithium levels in tap water and mental health problems in adolescents.¹

Between 2008 and 2009, investigators conducted a school-based cross-sectional survey in a Japanese prefecture. Students in 24 public junior high schools completed an anonymous self-report questionnaire, and researchers analyzed lithium levels in the schools’ drinking water. The response rate was 91.8%, with a total of 3040 students completing questionnaires.

Lithium levels in tap water ranged from 0.01 to 2.10 µg/L. In a multivariable regression analysis, lithium levels in the water were inversely correlated with depressive symptoms (P = .02) and interpersonal violence (P = .02), but not with suicidal behaviors. The authors speculate that lithium’s neuroprotective properties could explain its apparent benefits.

IN BRIEF

To reduce problems of polypharmacy, drug interactions, and adverse drug reactions, the Beers Criteria for Potentially Inappropriate Medication Use in Older Adults emphasizes prescribing only medications that are necessary (American Geriatrics Society 2015 Beers Criteria Update Expert Panel. J Am Geriatr Soc 2015;63[11]:2227-2246). Each time these criteria have been updated, the number of psychotropic medications considered potentially inappropriate for elderly patients has increased. Maust and others used data from an annual survey of office-based physicians to look at trends in the prescription of central nervous system (CNS) medications for almost 100,000 outpatients aged 65 years or older (JAMA Int Med 2017 Feb 13, Epub ahead of print). In particular, they assessed CNS polypharmacy visits, defined in the Beers criteria as a visit involving the initiation or continuation of three or more of the following medications: antipsychotics, benzodiazepines, nonbenzodiazepine benzodiazepine-receptor agonists, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and opioids. Between 2004 and 2013, annual visits involving CNS polypharmacy increased from 1.50 million to 3.68 million (from 0.6% to 1.4% of total visits; P < .001). The largest increase in CNS polypharmacy was among rural patients. CNS polypharmacy was most common for patients with anxiety, insomnia, or depression, but there was no significant increase at visits involving these diagnoses. By contrast, CNS polypharmacy increased significantly for patients with a diagnosis of pain. CNS polypharmacy also grew significantly for patients without a diagnosis of pain, insomnia, or other mental health diagnoses (P < .001), accounting for almost half of all such visits in 2011 to 2013 (45.9%).

Kil-Drori and colleagues recently conducted the first population-based study of the association between prolactin-elevating antipsychotics and the risk of endometrial cancer (J Clin Psychiatry 2017 Feb 14, Epub ahead of print). Hyperprolactinemia is a known adverse effect of all first-generation and some second-generation antipsychotics, and patients with endometrial cancer have been found to have elevated prolactin levels. First-generation antipsychotics were associated with a fivefold increased risk of endometrial cancer in one observational study (Yamazawa et al. Oncology 2003;64[2]:116-123), but antipsychotic users were compared with never-users in this trial, so confounding by indication may have been a factor. Kil-Drori’s group analyzed data from more than 65,000 women newly prescribed antipsychotic drugs from 1990 to 2013 and followed until 2014. During the follow-up period, 139 incident cases of endometrial cancer were identified (38.0 cases per 100,000 person-years). No significant difference was found in the risk of endometrial cancer between patients taking prolactin-sparing antipsychotics and those taking prolactin-elevating antipsychotics. In addition, there was no duration-response relationship in terms of cumulative duration of use. The investigators conclude that antipsychotic-induced hyperprolactinemia is not an important uterine carcinogen.

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Dr Ando’s group draws two implications from their results. First, if future research supports its safety, a possible public health strategy might entail promoting the intake of lithium-rich foods and water to mitigate behavioral problems in youth. Second, clinicians may want to consider prescribing low-dose lithium to treat depressive and aggressive symptoms in adolescents. A cross-sectional study like this one, although not definitive, is suggestive and intriguing. It can point the way to future investigation of a major public health issue.

DIET AND DEPRESSION: MORE DATA

Growing evidence across countries, genders, and age groups suggests that diet quality can improve or worsen health throughout the body—including the heart and brain. Healthy diets, like the Mediterranean diet, are high in plant foods (eg, vegetables, fruits, legumes, and whole grains) and lean animal protein, such as fish. Diets that are higher in processed foods and sugars, by contrast, appear to increase the risk of multiple diseases. With funding from their government, Jacka et al in Australia conducted a 12-week, randomized controlled trial called Supporting the Modification of Lifestyles in Lowered Emotional States (SMILES) to assess the efficacy of a modified Mediterranean diet as part of treatment for major depressive episodes.1

In parallel-group, single-blind fashion, adults with moderate to severe major depressive episodes were randomized to receive either dietary support (N = 33) or social support (N = 34), in addition to whatever psychotherapy or medication they were already receiving. Dietary support consisted of seven individual 1-hour sessions with a dietician. Social support employed a manual-based “befriending” protocol, with sessions on the same schedule.

From baseline until week 12, depression scores of patients in the dietary support group improved significantly more than those of the control group (P < .001). Moreover, at 12 weeks, 32.3% of the dietary support group but only 8.0% of the social support group had achieved remission (P = 0.028). These effects appeared to be independent of changes in body mass index, self-efficacy, smoking rates, or physical activity.

The authors cite various theories about the potential mechanism of the diet-brain connection, including brain plasticity, gut microbiota, and inflammatory and oxidative stress pathways.4 They hope for replication of their findings in larger samples. While we await further research in this area, it would be prudent to counsel psychiatric patients today—including those with depression—on how to progress toward a healthier diet.