This issue of the Residents' Journal focuses on the topic of advances in antidepressant therapy. In an editorial, Samuel T. Wilkinson, M.D., discusses the renewed search for new targets and treatments for major depressive disorder. In a review article, Sandarsh Surya, M.B.B.S., and Neil Mori, M.D., examine recent evidence for methods designed to maximize the therapeutic benefit of ECT, minimizing side effects and preventing relapse. Mahalia L. Way, M.D., Ph.D., analyzes clinical trials of the use of ketamine infusion for the treatment of depression. Stanley Lyndon, M.D., explores low-field magnetic stimulation as a potential treatment modality. In a treatment in psychiatry article, Laurel D. Pellegrino, M.D., outlines current recommendations for treating major depression with psychotic features, including discussion of relapse rates with antidepressant monotherapy and with antipsychotic therapy, as well as ongoing research. Lastly, Meredith Brandon, M.D., describes a case of drug reaction with eosinophilia and systemic symptoms during sertraline and aripiprazole treatment in an adolescent patient.
Major Depressive Disorder: The Renewed Search for New Targets and Treatments

Samuel T. Wilkinson, M.D.

Major depressive disorder is the most common mental illness and accounts for significant morbidity and mortality throughout the United States and the world (1). Results from the Sequenced Treatment Alternatives to Relieve Depression trials have demonstrated that our most commonly used treatments are only marginally effective and generally take weeks before any antidepressant effects are experienced. Hence, there is an urgent need for the development of better and faster treatments. To this end, the National Institute of Mental Health (NIMH) has funded the Rapidly-Acting Treatments for Treatment-Resistant Depression initiative, a multicenter research project aimed at developing faster therapies to relieve depression. The Rapidly-Acting Treatments for Treatment-Resistant Depression project involves advancing our understanding and potential utility of ketamine (trial NCT01920555), an N-methyl-d-aspartic acid (NMDA) receptor antagonist that has powerful and rapid antidepressant effects (2). Low-field magnetic stimulation, a noninvasive form of brain stimulation that has been shown to induce rapid elevation of mood in bipolar depression with minimal side effects (3), is also being studied as part of the Rapidly-Acting Treatments for Treatment-Resistant Depression initiative (trial NCT01654796). This initiative aims to investigate the potential of a number of other compounds with novel mechanisms, including thyrotropin-releasing hormone, allosteric modulators of alpha-amino-3-hydroxy-5-methylisoxazole-4-propionate receptors, and other NMDA receptor antagonists, as well as nonpharmacologic mechanisms (i.e., sleep deprivation, electroconvulsive therapy).

Historically, the development of drugs has been expensive and time-consuming. Hence, the NIMH is also sponsoring the Fast-Fail Trials initiative, which aims to expedite the development of medications used to treat major depressive disorder and other disorders. Because so many drugs are simply modifications of existing therapies that utilize the same mechanism (i.e., increasing synaptic concentrations of monoamine neurotransmitters), the project will also attempt to identify new brain targets for potentially novel therapeutic mechanisms. The consortium hopes to accomplish these objectives by utilizing relatively small clinical trials (N=10–30) and by studying candidate compounds in humans, rather than animals. One of the first such trials involves investigating the potential of a kappa opioid receptor agonist (trial NCT02218775) in treating anhedonia.

Another potential approach to combating major depressive disorder involves the concept that some biological treatments induce a state of neuroplasticity or rapid antidepressant effects. Low-field magnetic stimulation, a noninvasive form of brain stimulation that has been shown to induce rapid elevation of mood in bipolar depression with minimal side effects (3), is also being studied as part of the Rapidly-Acting Treatments for Treatment-Resistant Depression initiative (trial NCT01654796). This initiative aims to investigate the potential of a number of other compounds with novel mechanisms, including thyrotropin-releasing hormone, allosteric modulators of alpha-amino-3-hydroxy-5-methylisoxazole-4-propionate receptors, and other NMDA receptor antagonists, as well as nonpharmacologic mechanisms (i.e., sleep deprivation, electroconvulsive therapy).

There is an urgent need for the development of better and faster treatments.

References


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Electroconvulsive therapy (ECT) is the most effective treatment for both unipolar and bipolar depression, with response rates of 80%–90% when used as first-line therapy and 50%–60% in treatment-resistant depression. ECT is often considered the best option for severe depression, particularly for depression with psychotic or catatonic features refractory to pharmacotherapy and psychotherapy because of its potential for rapid alleviation of symptoms (1). Additionally, ECT is one of a short list of treatments that can significantly reduce suicidality. ECT can be considered a first-line treatment option for patients with severe depression coupled with psychotic features, catatonia, suicide risk, or food refusal leading to nutritional compromise, for patients for whom a rapid antidepressant response is required, for patients who have previously shown a positive response, and for patients who prefer it (1). Pregnant women with pharmacotherapy-resistant depression with psychotic or catatonic features and pregnant women who prefer the treatment can be offered ECT (1). Severe depression with comorbid general medical conditions that preclude the use of antidepressants should also be considered for ECT (1).

The practice of ECT has been progressively evolving since its initial emergence in the 1930s. In the present review, we discuss recent evidence for methods to maximize ECT’s therapeutic benefit, minimize its side effects, and prevent relapse.

**Electrode Placement**

**Bitemporal ECT**

The position of the electrodes used to deliver energy has a significant impact on both efficacy and side effects of the treatment. The bitemporal montage has been used since the origin of ECT and is still considered the gold standard when comparing efficacy and side effects with other types of montages (2). In bitemporal ECT, electrodes are placed on both temples of the skull, which correspond to the point just above the midpoint on an imaginary line connecting the outer canthus of an eye and the external auditory meatus (Figure 1A). Cognitive impairment is the major limitation associated with bitemporal ECT, thought to be due to the direct effect on the dominant medial temporal lobe. In the 1970s, d’Elia introduced right unilateral ECT to minimize cognitive side effects, and it is now the second most commonly used montage (2). In right unilateral ECT, one electrode is placed on a point just to the right of the point of intersection between a perpendicular line connecting two external auditory canals and a line connecting the nasion and inion, and the second electrode site is similar to that of bitemporal ECT on the right side (Figure 1B). The initially proposed “low-dose” energy setting used with right unilateral ECT is associated with poor antidepressant response rates, and current literature suggests that high-dose right unilateral ECT has a comparable efficacy to moderate-dose bitemporal ECT and retains cognitive advantages (3). Some of the new montages being explored to retain the efficacy of the treatment and diminish cognitive side effects are discussed below, although the data are limited.

**Bifrontal ECT**

Bifrontal ECT became popular in the 1990s and is now the third most commonly used montage. The bifrontal montage involves placing the electrodes 5 cm above the lateral angle of the orbits (Figure 1C) (4). Studies exploring the efficacy of bifrontal ECT have yielded mixed results. One initial randomized controlled trial of 59 patients with a major depressive episode reported that bifrontal ECT had better therapeutic efficacy compared with bitemporal and right unilateral ECT (4). However, further study in a recent large randomized controlled trial of 230 patients with unipolar and bipolar depression did not replicate the findings and found that the speed of response was greater in the bitemporal group (5). In terms of cognitive profile, a meta-analysis reported that bifrontal ECT had a small but statistically significant benefit regarding global cognition scores compared with bitemporal ECT and an effect comparable to right unilateral ECT (6). Additionally, bifrontal ECT had a smaller decline in visual memory, greater decline in immediate verbal memory, and no difference in frontal executive functioning compared with right unilateral ECT.

**Left Anterior Right Temporal ECT**

Swartz and Nelson (7) introduced the left anterior right temporal montage, in which the right-side electrode is placed at the right bitemporal electrode site and the left-side electrode is placed 5 cm anterior to the left bitemporal electrode site (Figure 1D). In small studies, left anterior right temporal ECT had comparable efficacy to bitemporal ECT, with better cognitive profiles (7). In a case series, three patients with chronic late-life depression, whose symptoms were not responsive to previously effective ECT treatments with bitemporal, right unilateral, or bifrontal montages, successfully responded to left anterior right temporal ECT (8). Changing to the left anterior right temporal montage during the maintenance phase also prevented relapse, improved quality of life, and, interestingly, improved the seizure quality in all three patients.
Focal Electrically Administered Seizure Therapy

Focal electrically administered seizure therapy is a novel form of ECT that differs from other montages in several ways (9). Two different-sized electrodes are used. A smaller anode (0.75 inches) is placed above the center of the right eyebrow, and a larger cathode (1×2.5 inches) is placed tangential to the midline and extended across the right supplementary motor cortex (Figure 1E). The stimulus used is a unidirectional direct current that flows from anode to cathode (Figure 1H). With this technique, the subcallosal cingulate gyrus and frontal pole, neuroanatomical targets of depression, are stimulated while avoiding the temporal lobes implicated in the cognitive impairment associated with ECT (10). In a feasibility study, focal electrically administered seizure therapy was safe, well-tolerated, and effective in the treatment of depression (10).

Stimulus Parameters

Stimulus parameters, such as waveform and total dose, can independently influence the efficacy of ECT and the severity of cognitive impairment (2). Sine waveform stimulus was the original waveform used in ECT but has long been abandoned due to its inferior efficacy and dramatically worse cognitive side effects (2). Alternating current pulses are conventionally used, and unidirectional direct current pulses are now being explored in the focal electrically administered seizure therapy technique (9, 10).

Stimulus dose is a product of pulse amplitude, pulse width, pulse frequency, and stimulus duration. Evidence suggests that stimulus dose is the strongest predictor of treatment outcome (2). Irrespective of the values of other parameters, higher stimulus dose tends to have better efficacy and poorer cognitive outcome compared with lower stimulus dose (2). Current guidelines recommend determining a threshold dose that can induce an EEG seizure of a 30-second duration for the first treatment (1). For subsequent treatments, recommended doses are 1.5–2.5 times the threshold for bitemporal ECT and 5–8 times the threshold for right unilateral ECT (2).

One aspect of the sine waveform believed to contribute to its poor cognitive side effects is its prolonged pulse width of 8.33 ms–10 ms (2). Brief pulse has a lower width of 0.5 ms–2 ms (Figure 1F), which is one of the proposed reasons for its improved cognitive profile (2). Recent research explores the use of stimulus with pulse widths of 0.2 ms–0.5 ms, termed ultra-brief pulse (Figure G). There is some controversy concerning the value of ultra-brief pulse, with several studies suggesting that it may be less efficacious or require more treatments to achieve remission when compared with standard brief pulse stimulation (11), and this difference seems to nullify when high-dose ultra-brief pulse stimulation is used and retains cognitive benefits (12, 13).

Anesthesia

Methohexital is generally considered the gold-standard induction agent in ECT anesthesia due to its rapid onset, short duration, good hemodynamic profile, low cost, and relatively low potential to increase seizure threshold (2). Propofol is the second most commonly used induction agent for ECT, with higher anticonvulsant properties but lower incidence of postictal agitation compared with methohexital (2). Emerging evidence suggests that low-dose ketamine infusion has an independent rapid antidepressant effect that lasts 2–3 days (14). As a result, several studies have examined the use of ketamine as an induction agent for ECT and whether it can offer an adjunctive antidepressant effect. A meta-analysis of four trials with 118 patients receiving ECT for unipolar and bipolar depressive illness reported significantly greater improvement of depression scores among patients receiving ketamine anesthesia compared with thiopental or propofol (14). However, ketamine administered in anesthetic doses is associated with higher rates of nausea, dizziness, psychotomimetic phenomena, and cardiovascular excitement. A longitudinal crossover study of 20 patients reported that ketamine inductions resulted in increased side effects, more subject drop out, and longer reorientation times compared with methohexital (15). Given the small sample sizes and heterogeneity of current evidence, it is premature to make conclusions about the benefit-to-risk ratio of the use of ketamine for ECT anesthesia.
Relapse Prevention

It has been well established that an acute course of ECT without any form of continuation treatment is associated with a high likelihood of depression relapse, estimated to be up to 80% within 6 months (16). With continuation pharmacotherapy, relapse rates drop to nearly 40% in 6 months and 50% in 12 months, and a recent meta-analysis reported that maintenance ECT resulted in similar 6-month relapse rates (16). With respect to medication strategies after successful ECT, a randomized controlled trial of 290 patients with unipolar depression found a 6-month relapse rate of 39% among patients receiving a combination of nortriptyline and lithium, compared with a rate of 60% in the nortriptyline-alone group and 84% in the placebo group (17).

A retrospective study reported an impressive 16% relapse rate within 6 months of successful ECT when an antidepressant plus lithium combination was used, whereas other combinations, such as antidepressants plus antipsychotics (75% relapse rate), antidepressants plus mood stabilizers other than lithium (69% relapse rate), and antidepressants only (60% relapse rate) (18), seemed to offer no additional benefit.

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References

Ketamine Infusion for the Treatment of Depression

Mahalia L. Way, M.D., Ph.D.

Ketamine is a noncompetitive antagonist of the N-methyl-d-aspartic acid (NMDA) receptor that has been repeatedly shown to have rapid but temporally limited antidepressant effects in both unipolar and bipolar depression. The present study is a review of the results of clinical trials of ketamine, the obstacles to the widespread use of ketamine, and the evolving understanding of its mechanism.

Efficacy

The first clinical trial of ketamine for the treatment of depression was a small, randomized placebo-controlled crossover trial of a single subanesthetic dose (0.5 mg/kg) administered intravenously over 40 minutes. The study found a robust antidepressant effect developing over 3 days following infusion, with levels returning to baseline in 1–2 weeks. These antidepressant effects temporally outlasted the euphoric effects of ketamine, which resolved within hours (1). Similar results were found in a slightly larger crossover study conducted in 2006 that tracked the timing of response more closely (2). The study found significant improvement within 110 minutes after infusion, with 71% of participants meeting response criteria and 29% meeting remission criteria at 24 hours. These effects were maintained for at least a week in 35% of responders. Numerous small studies have reported similarly robust results, with response rates ranging from 25% to 85% at 24 hours and 14% to 72% at 72 hours (3, 4), but all of these studies used inert placebos, which may have interfered with blinding and lowered placebo response scores. The largest trial to date was a two-site randomized controlled trial examining 72 patients with treatment-resistant major depression using midazolam (0.045 mg/kg) as an active placebo (5). At 24 hours postinfusion, the response rate to ketamine was 74%, while that of midazolam was 28% (odds ratio=2.18, 95% confidence interval [CI]=1.21–4.14), and ketamine resulted in lowered scores on the Montgomery-Åsberg Depression Rating Scale by almost 8 points more than midazolam (7.95 points, 95% CI=3.20–12.71), representing a large effect size (Cohen’s d=0.81). The Montgomery-Åsberg Depression Rating Scale scores of both groups (ketamine, midazolam) began increasing with time around day 3, with similar trajectories, and by day 7 scores on the Montgomery-Åsberg Depression Rating Scale and Quick Inventory of Depressive Symptomatology-Self Report no longer demonstrated any statistically significant differences between the groups. By day 17 postinfusion, 60% of the ketamine responders had relapsed, but the rest maintained some improvement through day 30. Trials of ketamine for bipolar depression have found similar results, with antidepressant effects generally not lasting more than 1–2 weeks (6, 7).

Safety

In the largest placebo-controlled study to date (5), the most common adverse events in the ketamine group were dizziness, blurred vision, headache, nausea, dry mouth, poor coordination, poor concentration, and restlessness. Seventeen percent of the ketamine patients experienced significant dissociative symptoms immediately after infusion, but these symptoms resolved within 2 hours, and none experienced psychotic symptoms. Infusion was halted for two patients: one of whom experienced elevated blood pressure unresponsive to beta blockers (maximum, 187 mmHg/91 mmHg), while the other experienced transient hypotension and bradycardia, which resolved without intervention. Transient cardiovascular effects are common, and at most academic research centers the patient’s vital signs are monitored throughout the infusion. In the two small crossover studies discussed above, adverse events included perceptual disturbances, confusion, hypertension, euphoria, dizziness, and increased libido, all of which resolved by 110 minutes (1, 2). Studies of ketamine for bipolar depression have shown a similar array of transient adverse events, with no shifts to mania (6, 7).

More concerning than the adverse events associated with infusion are the unknown long-term consequences of chronic use and the potential for ketamine abuse, given its history as a club drug (8, 4). When abused, ketamine is associated with cystitis and biliary dilation, but users are often taking multiple drugs at once and using ketamine at higher and more frequent doses than what is normally used for depression (9). Ketamine is known to have opioid receptor activity, but animal studies of whether it is reinforcing, resulting in drug-seeking behaviors, have been mixed (10, 8). The S-enantiomer of ketamine appears to have less psychomimetic effects than the R-enantiomer, but it is unclear whether this would decrease its abuse potential (8).

Increasing Duration

Attempts to increase the duration of ketamine’s antidepressant effects have been met with only modest success. Although open-label case reports have found that repeated ketamine infusions can extend benefits for several months (11), larger studies have shown more modest results. A small study of responders who received five additional infusions on a schedule similar to that for ECT found that 8/9 relapsed within 30 days (12), and Murrough et al. (13) found that antidepressant effects lasted an average of 18 days. Attempts to follow ketamine infusion with oral riluzole, which modulates glutamate and increases neuroplasticity, were unsuccessful (4, 14). Which oral antidepressants work best following ketamine treatment is unknown and may be difficult to determine, given the fact that most patients receiving ketamine have already failed multiple antidepressant trials.
Ketamine for Suicidal Ideation

The limited duration of ketamine’s antidepressant effects, the unknown consequences of its chronic use, and known abuse potential are obstacles to intravenous ketamine becoming a common treatment for depression. However, its rapid onset and robust antidepressant effects after a single dose, with relatively mild, transient adverse effects, make it a good candidate for the acute treatment of suicidality. All of the studies discussed above found a statistically significant decrease in the suicidal ideation items of their depression instruments used. Diazgranados et al. (15) found that the suicidal ideation score, as measured by the Scale for Suicidal Ideation, dropped within 40 minutes of infusion and remained improved for up to 4 hours. Other studies have found that suicidal ideation remained significantly lower for several weeks (12), potentially long enough to allow other interventions to have an effect. To the best of our knowledge, there has been only one trial of intravenous ketamine for suicidal ideation in an emergency department to date (16), but this study was conducted without controls, making it difficult to compare ketamine with other potential interventions. Several other studies evaluating ketamine for suicidal ideation in emergent settings are in process (ClinicalTrials.gov identifiers: NCT01209845, NCT01892995, NCT02183272).

Mechanism of Action

From its earliest studies, the timing of ketamine’s effects has suggested that events downstream of the initial NMDA receptor blockade were responsible for its antidepressant action. Ketamine’s psychotomimetic and dissociative effects peak around 30–40 minutes postinfusion but no longer exist before its antidepressant effects emerge (1,2,4,17). Experiments interrupting the cascade of events initiated by NMDA receptor blockade have begun to shed light on the mechanism of ketamine’s antidepressant effect and offer new avenues for research.

Rodent models have demonstrated a three-stage response to ketamine. First, ketamine blocks the presynaptic NMDA receptors that would normally inhibit the release of glutamate. The resulting glutamate surge increases activation of postsynaptic AMPA receptors, which in turn activate neuroplasticity-related signaling pathways resulting in synaptogenesis and potentiation (17). The mammalian target of rapamycin complex 1 (mTORC1), which regulates the initiation of protein synthesis, and brain-derived neurotrophic factor (BDNF) are essential components of these pathways and necessary for the antidepressant effects of ketamine to take place. Blocking AMPA receptors, interfering with mTORC1, or interfering with the effectiveness of BDNF all can prevent the rapid antidepressant effects of ketamine in animal models (17–20). Li et al. (18) showed that when these pathways are intact, ketamine induces the rapid induction of mature spines in layer V pyramidal neurons in the prefrontal cortex. It also causes an increase in the frequency and amplitude of the 5-HT and hypocretin-induced excitatory postsynaptic currents that mark increases in corticocortical and thalamocortical connections. In the Li et al. study, these neuroplastic changes lasted about 7 days and were accompanied by improvements on several different rodent models of depression and anxiety. This correlation of neuroplastic and behavioral changes in animals is consistent with postmortem findings in humans, in which depression is associated with decreased prefrontal synaptic connectivity and neuronal atrophy and synaptic depression in the prefrontal cortex and hippocampus. Patients with depression have also been found to have lower levels of central and peripheral BDNF, and attenuating polymorphisms in the BDNF receptor are also associated with depression. Since traditional antidepressants increase BDNF and synaptogenesis, it is not surprising that a rapid-acting antidepressant would do the same (17).

Summary

Ketamine is a rapid-acting noncompetitive NMDA antagonist with robust antidepressant effects that begin after its psychotomimetic effects have worn off, lasting 1–2 weeks after a single infusion. Attempts to prolong the antidepressant effects of ketamine by repeated infusions and the use of adjunctive medications have met with mixed results. Although the side effects of subanesthetic doses of ketamine are mild and transient, the unknown consequences of prolonged use, the ephemeral nature of its antidepressant properties, and its history as a drug of abuse are obstacles to it becoming a mainstream treatment for depression. However, its rapid, robust action may be useful in the treatment of acute suicidality and as a bridging strategy while awaiting the effects of longer-acting traditional antidepressant therapies. Our growing knowledge of the mechanism of ketamine presents new targets for the development of future antidepressants, including AMPA receptors, mTOR, BDNF, and other proteins involved in the restoration of the neuronal circuitry impaired by depression.

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Low-Field Magnetic Stimulation: The Next Big Thing?

Stanley Lyndon, M.D.

Depression has a lifetime prevalence of approximately 17% in the United States (1), and approximately 30% of patients do not achieve remission after four different adequate and sequential antidepressant treatment trials (2). Many of the currently available treatment modalities, including medications, electroconvulsive therapy (ECT), and repetitive transcranial magnetic stimulation (rTMS), have one major common limitation: a very slow onset of therapeutic effect (3, 4). Although rapid relief (within hours) has been reported with intravenous ketamine and deep brain stimulation, studies to date have shown either that these rapid responses are transient (in the case of ketamine) or the treatment involves substantial perioperative risks, including intracranial infection or hemorrhage (in the case of deep brain stimulation). Low-field magnetic stimulation is a fairly new potential treatment modality that uses a small, portable tabletop device to achieve rapid improvements in mood in as little as 20 minutes (5). While the durability of these effects is yet to be studied, and the preliminary results need to be interpreted with utmost caution, the rapidity of mood elevation achieved using a portable device that could someday be used by an acutely depressed and suicidal patient at home with at least temporary relief provides much cause for excitement at this time.

Rapid improvements in mood were first observed fortuitously when patients with bipolar depression underwent an experimental magnetic resonance spectroscopic imaging procedure (6). A small, sham-controlled pilot study was then designed to check whether the findings could be replicated in patients with bipolar depression, and it showed promising results (7). Antidepressant-like behavioral effects of low-field magnetic stimulation were then demonstrated using the forced swim test in rats, which is one of the animal models traditionally used to demonstrate responses to antidepressant treatments (8). Following these successes, a portable low-field magnetic stimulation device that produced the same time-varying electromagnetic fields that were within clinical MRI guidelines but that differed in waveform, frequency, and strength from MRI was built and used by Rohan et al. (5) in their recent study involving patients with a current depressive episode.

The stimulation paradigm utilized consisted of a 1-kHz oscillating magnetic field, adapted from the component of the original MRI protocol, producing electric fields of 1 V/m or less. This differs significantly from the other electromagnetic treatments currently used for the treatment of depression. For instance, ECT produces electric fields larger than 200 V/m, while rTMS and deep brain stimulation produce fields of approximately 100 V/m, which are of sufficient magnitude to directly induce neuronal depolarization (9). The oscillations in rTMS and deep brain stimulation are also at the much lower frequencies of 10 Hz and 120 Hz, respectively; ECT has a frequency of approximately 40 Hz–60 Hz. That low-field magnetic stimulation would have similar clinical effects as the other electromagnetic treatments despite inducing a drastically different field is another reason to be excited, as it could not only provide us methods to influence neuronal activity without directly depolarizing neurons but also help us gain better insight into the pathophysiology of depression, an entity still not fully understood.

In the most recent study by Rohan et al. (5), low-field magnetic stimulation was applied in a double-blind sham-controlled design in a group of 63 patients with a current episode of depression and a diagnosis of either major depressive disorder or bipolar depression. Effects on mood were assessed primarily using a self-rated visual analog scale and the observer-rated 17-item Hamilton Depression Rating Scale (HAM-D) and secondarily using the self-rated Positive and Negative Affect Schedule. The authors found that low-field magnetic stimulation produced an immediate improvement on all scales except the Positive and Negative Affect Schedule negative affect (changes in the Positive and Negative Affect Schedule positive affect scores were significant) across the combined population of depressed patients compared with sham treatment. The significance of the results is amplified by the notable advantage of low-field magnetic stimulation compared with the other neuromodulation techniques: the absence of any physical sensation with stimulation, enabling excellent blinding (the mild operational sounds produced by the magnetic coil are easily duplicated in the sham arm). Low-field magnetic stimulation is also completely noninvasive, with no known adverse effects.

However, there are a number of issues that cloud the significance of the results. Most importantly, the study was not designed to measure the durability of mood improvement but rather to isolate the electromagnetic field responsible for the earlier observations of rapid mood elevating effects of low-field magnetic stimulation. Mood changes were evaluated immediately after the intervention, and although the participants were contacted 1 week later to assess for adverse effects, no subsequent assessments were conducted to determine whether the antidepressant effects persisted after the first hour. Also concerning is the unclear validity of the scales used to measure mood changes over very short periods of time. HAM-D, for instance, has several items that require the observer to assess the subject’s symptoms of depression over the past 1 week. The scale has not been validated for shorter periods of time, and it is difficult to know what the reported changes in those items actually mean when administered less than an hour apart.

Another criticism of the Rohan et al. study is the relatively small size and
heterogeneity of the tested population, considering that the study included patients with bipolar disorder as well as major depressive disorder, as defined by DSM. The initial analysis with the groups stratified into the two disorders also did not show statistical significance with treatment, and the authors had to combine data across the diagnostic groups for the results to reach statistical significance. However, considering the recent criticisms of the nosological approach of DSM (10) and the National Institute of Mental Health’s strong push toward Research Domain Criteria over DSM (11), as well as the small number of subjects in the stratified groups that could impede gaining meaningful correlations, this criticism may be unwarranted.

Unlike rTMS and deep brain stimulation, low-field magnetic stimulation does not target a specific region of the brain. Because of this widespread approach, it is difficult to determine the exact mechanism by which low-field magnetic stimulation exerts its effects. It is also important to assess whether or not specific neuroanatomical structures or networks might be mediating the observed effects, since identifying them would be the *sine qua non* of transitioning to larger clinical trials to assess treatment efficacy, at least according to NIMH’s recent guidelines requiring future trial proposals to identify a defined neurobiologic target or mediator. It was postulated that the effects seen in low-field magnetic stimulation may stem from changes in the membrane potentials of the dendritic neurons in layers 5 and 6 of the cortex, since these were shown to be involved in mood regulation (12). As acknowledged by the authors, these possibilities regarding the mechanism and site of action are only speculative until tested. Another study showed significant reductions in the glucose metabolism in several regions of the cerebral cortex following exposure to low-field magnetic stimulation compared with sham treatment in healthy volunteers (13). Connectivity between cortical regions most strongly penetrated by low-field magnetic stimulation fields has also been shown to be increased in depression (14) and decreased with treatment (15). Therefore, further research into the mechanisms of action, as well as determining whether or not applying a global magnetic field that affects a wide group of important cortical brain structures is warranted over identifying the specific regions responsible for the observed effects and applying the field only to those regions, is ultimately necessary moving forward.

Despite the uncertainties, however, the results described in the Rohan et al. (5) study are fascinating, especially considering the uniqueness of low-field magnetic stimulation among the neuromodulatory techniques in terms of the mechanism and the effects. And as it is unclear whether the various neuromodulatory techniques exert their antidepressant effects through a common mechanism or multiple mechanisms, there is also the possibility of combining various methods of neuromodulation in the treatment of depression in the future. Other potential areas of research include testing combinations of neuromodulation, psychotherapy, and pharmacological therapy in the treatment of depression, while at the same time observing the neural networks and substrates modulated by them during the treatment to understand the underlying disease process better. If the preliminary results of low-field magnetic stimulation could be replicated in larger, independent studies, preferably with a durable effect, low-field magnetic stimulation could very well become the “next big thing” in the treatment of depression.

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**References**


A Question of Balance: Preventing Relapse of Psychotic Depression

Case
A man with major depression and suicidal ideation is treated for psychotic symptoms.

“Mr. E” is a 35-year-old man who was admitted to the inpatient psychiatric unit for a major depressive episode and suicidal ideation with a plan to overdose (he had stock-piled pills). His presentation was notable for significant psychomotor retardation. He was cooperative but guarded, citing a need to maintain his privacy. The patient was started on mirtazapine (15 mg) for depression and insomnia. On the third day of hospitalization, he expressed worry that his dreams were coming true. Before being hospitalized, he had a dream that involved being back in the military, being tortured, winding up in a hospital, and facing a large spider. Because he was now in the hospital, he was afraid that other parts of his dream might also come true. On the fourth day of hospitalization, he admitted hearing voices telling him to leave the hospital and take his life. Aripiprazole was added to his regimen and titrated up to 10 mg; his psychotic symptoms and mood improved after 5 days of treatment. The patient was discharged and scheduled to follow-up in the outpatient clinic within a week.

If you were Mr. E’s outpatient provider, how long would you continue treating him with aripiprazole? He was already overweight and had an elevated lipid profile, and thus treating him for longer than necessary could compromise his physical health. On the other hand, discontinuing aripiprazole too soon could result in relapse of his depressive and psychotic symptoms, as well as his suicidality.

Factors to Weigh
Major depression with psychotic features is a debilitating form of depression, with high morbidity and mortality. Compared with patients with nonpsychotic depression, those with psychotic symptoms experience a higher depressive symptom burden, a longer time to recovery (1), a higher rate of relapse (2), and a mortality rate that is twice as high (3). One large epidemiologic study estimated that almost 20% of people with major depression have psychotic symptoms (4). This percentage is even higher in the elderly, estimated in one study to be 47% (5).

Current APA practice guidelines for treatment of psychotic depression recommend acute-phase treatment with either electroconvulsive therapy (ECT) or a combination of an antidepressant and an antipsychotic (6). However, less evidence exists to support recommendations for maintenance treatment or the choice of medication and length of therapy following remission of acute symptoms. Unnecessary treatment with antipsychotics disposes patients to potentially serious side effects, but undertreatment of this serious disorder poses the risk of relapse. Ideal maintenance treatment would balance these opposing factors while keeping the patient well.

Relapse
Relapse Rates With Antidepressant Monotherapy
Four studies have followed patients maintained on antidepressant therapy alone, and these studies found variable rates of relapse, from 27% to 70%. The highest rate (70%) was found in a study of patients maintained on stable doses of antidepressant therapy for a mean of 3.5 years following ECT treatment of the initial episode (7). Two other studies found rates of about 50%. One of these studies followed 19 patients who were treated with nortriptyline for 2 years, and 47.4% of these patients had either a relapse or a recurrence (2). The second study found a relapse rate of 50% among 32 patients taking antidepressants (primarily tricyclics) for 1 year following ECT treatment (8). Finally, the study with the lowest relapse rate (27%) was a prospective study of 30 adults treated with fluoxetine and perphenazine, then maintained on fluoxetine alone for 1 year (9).

Factors Associated With Relapse
Several factors explain the variability in observed relapse rates. First, studies with longer follow-up tended to report more relapse events, which may represent the course of this illness over time. More standardized follow-up periods in future studies could correct for this problem. Second, the choice of antidepressants used during the maintenance phase may have affected relapse rates. Fluoxetine was the antidepressant used in the study with the lowest relapse rate, while the studies with higher relapse rates tended to use tricyclic antidepressants. In nonpsychotic depressed patients who have been treated with ECT, treatment with paroxetine was more protective against relapse than imipramine (10); it is possible that the same is true for psychotic depression. Third, the choice of treatment during the acute phase may have influenced outcomes during maintenance treatment. Pharmacotherapy was the choice of acute-phase treatment in the study with the lowest relapse rate (9), while ECT was used in the studies with...
higher rates (2, 7, 8). In fact, when Flint et al. (2) broke down patients by acute-phase treatment, those treated with ECT had a 53.3% rate of relapse, while those treated with pharmacotherapy had a rate of 25% (although the difference between these two groups was not statistically significant). One explanation for this phenomenon is that ECT tends to be reserved for more severely ill patients, and thus patients initially treated with ECT may have had a poorer prognosis.

Relapse Rates When Antipsychotic Therapy is Prolonged
One small study (N=10) suggests that long-term combination pharmacotherapy can prevent relapse. Of patients followed for a mean duration of 11 months, 80% maintained remission on a combination of antidepressant and antipsychotic treatment. The patients who relapsed did so after discontinuing their medications (11). This finding is limited by the lack of a control group and the variability of medications and doses used.

There is only one randomized controlled trial comparing antidepressant maintenance treatment alone with combination treatment with an antipsychotic. For this study, 28 older adults (age 50–84 years) were randomly assigned to maintenance treatment with either nortriptyline (target blood concentration, 50 ng/ml–150 ng/ml) and perphenazine (target dose 12 mg–16 mg) or nortriptyline and placebo for 26 weeks. About 25% of patients in both groups experienced a relapse, with no difference between groups. These results were surprising, since the authors anticipated that the group receiving combination treatment would have a lower rate of relapse. It is unclear whether this finding pertains only to older adults or would be true for younger adults as well, and thus more data are needed.

An additional finding of this study was that the group receiving combination treatment experienced a higher degree of side effects with significant morbidity, including extrapyramidal side effects, tardive dyskinesia, and falls (12). Thus, this study serves as a good example of a case in which the risks of longer treatment with an antipsychotic outweighed the benefits for a given population.

It would perhaps be most efficacious to determine whether there are characteristics of individuals that determine who needs to be treated longer and who does not. Toward this end, Rothschild et al. (9) identified some characteristics of patients who relapsed. They found that patients who relapsed on antidepressant therapy alone tended to have had longer initial depressive episodes and more frequent past episodes. Along similar lines, Spiker et al. (8) found that patients who relapsed tended to have longer initial episodes, but this finding did not reach statistical significance.

Ongoing Research
The STOP-PD II (Sustaining Remission of Psychotic Depression II) group is currently addressing the best approach to maintenance treatment, which will be the largest maintenance study to date. An earlier STOP-PD study (13) compared acute-phase treatments of olanzapine (target dose 15 mg–20 mg) and sertraline (target dose 150 mg–200 mg) with olanzapine and placebo and found that combination treatment was associated with higher rates of remission (41.9% vs. 23.9%).

The current STOP-PD II study is evaluating maintenance treatment following 20 weeks of acute-phase treatment (14). Subjects whose symptoms remit will be randomly assigned to receive either sertraline and olanzapine or sertraline and placebo for 36 weeks (at the same doses used for acute treatment). The primary outcome to be measured is relapse rate, with relapse defined as a subject experiencing a resurgence of depressive or psychotic symptoms, a suicide plan or attempt, mania or hypomania, or psychiatric hospitalization due to any of the above. Metabolic changes will be examined as a secondary outcome. Additionally, the authors will investigate age and genetic polymorphisms as possible predictors of variability in response to treatment, which could potentially lead to more personalized treatment.

Recommendations for Treatment
Because of the many unanswered questions about maintenance treatment of psychotic depression, outpatient providers could follow an algorithm for treating psychotic depression created by Dr. Rothschild (15) that is based on existing research. His recommendations for maintenance treatment include continuing the administration of an antipsychotic for 4 months following remission of symptoms, followed by a very gradual taper. In an example, he treats a patient with sertraline (150 mg) and olanzapine (15 mg). He monitors psychotic symptoms with the Brief Psychotic Rating Scale and depressive symptoms with the Hamilton Depression Rating Scale. After 4 months of treatment following remission of symptoms, he tapers olanzapine by 5 mg every 4 weeks. However, if a patient experiences significant side effects during treatment, he suggests starting the taper sooner. He continues sertraline indefinitely (15).

Dr. Pellegrino is a second-year resident in the Department of Psychiatry, University of Washington, Seattle.

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References


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Case Report

DRESS Syndrome Induced by Antidepressant Sertraline

Selective serotonin reuptake inhibitors (SSRIs) are associated with notable side effects, including gastrointestinal disturbances, headaches, sexual dysfunction, insomnia or sedation, sweating, and bleeding. Less commonly, however, are dermatologic symptoms. In cases of treatment-resistant depression, SSRIs are combined with atypical antipsychotics such as aripiprazole or quetiapine, which also carry little to no risk of dermatologic reactions. The present case involves a 14-year-old adolescent who developed drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome during the use of sertraline and aripiprazole. To the best of our knowledge, there are no other documented cases of DRESS syndrome induced by either sertraline or aripiprazole.

Case

“Meghan” is a healthy 14-year-old adolescent with a psychiatric history of depression and anxiety, who was hospitalized after presenting with complaints of a new-onset generalized, erythematous, and pruritic rash. The rash started 2 weeks prior to admission and initially only involved her thighs but then spread to her arms, face, back, and abdomen. She also developed bilateral hand swelling and paresthesias in her hands and feet. The patient reported that sertraline (100 mg daily) was started 4 months earlier for depression, and approximately 1 month later, aripiprazole (2 mg daily) was added to the regimen for antidepressant augmentation. After evaluation by an outpatient dermatologist and following a biopsy, she was diagnosed with dermohypersensitivity, most likely due to an allergic reaction from sertraline and/or aripiprazole. Because the patient was tapered off both medications by her outpatient psychiatrist, she was also treated with oral prednisone, with no improvement of the rash. On presentation to the emergency department, her vital signs were stable and her laboratory results were significant for a leukocytosis of 15,200/mm² and eosinophilia of 11.5%. During her hospitalization, she was treated with intravenous prednisone, diphenhydramine, and hydroxyzine and underwent daily hydrotherapy. Based on her clinical presentation and histological confirmation, she was diagnosed with DRESS syndrome. After 6 days, the rash improved, and the patient was discharged home.

Discussion

DRESS syndrome is a rare, potentially life-threatening drug-induced hypersensitivity reaction that includes skin eruption, hematologic abnormalities (eosinophilia and atypical lymphocytosis), lymphadenopathy, and internal organ involvement (liver, kidney, and lung) (1–3). The diagnosis of DRESS syndrome is based upon the combination of clinical features (history of drug exposure), cutaneous findings, systemic findings (fever, lymphadenopathy, and visceral involvement), laboratory findings such as leukocytosis with eosinophilia >700/μL and/or atypical lymphocytosis, and histologic findings. DRESS syndrome is primarily a drug-specific immune reaction caused by latent viral reactivation of various herpes viruses (4). The reaction usually begins 2–6 weeks after the initiation of the offending medication (5, 6). Antiepileptic agents and allopurinol are the most frequently reported causes. Identification and prompt withdrawal of the offending drug is the mainstay of treatment (3).

In the above case, the diagnosis of DRESS syndrome was confirmed both clinically and histologically. The antidepressant sertraline was most likely the causative agent because there are no reports of associated rash with aripiprazole in the literature (7, 8). Furthermore, DRESS syndrome has been associated with the use of antidepressants such as desipramine, amitriptyline, and fluoxetine (9).

Conclusions

DRESS syndrome is a potentially life-threatening adverse drug reaction that can be infrequently induced by some of the most commonly prescribed antidepressant medications. This case highlights that although antidepressants such as SSRIs are considered to be relatively benign in terms of side effects, it is essential that clinicians are still able to recognize more serious side effects. Perhaps more research in dermatologic manifestations of antidepressant medications and greater information availability on the potential dermatologic side effects would help reduce such occurrences.

Dr. Brandon is a third-year resident at Rutgers-New Jersey Medical School, Newark, N.J.

References

4. Takahashi R, Kano Y, Yamazaki Y, et al: Defective regulatory T cells in patients with severe drug eruptions: timing of the dysfunction is associated with the patho-


Infanticide, the intentional killing of a child less than 1 year of age, has been practiced throughout history for a variety of reasons, including presence of disability, gender selection, and population control (1). In 2011, the Centers for Disease Control and Prevention estimated the number of infant deaths due to homicide to be at 7.3 per 100,000, excluding those deaths in which intention was unknown (2). Additionally, the World Health Organization estimated the international rate of deaths due to violence against children ages 0 to 4 years to be 136 per 100,000 in 2008, excluding deaths occurring during war (3). The continued gravity of this issue and potential involvement of parental mental illnesses warrant examination of infanticide literature to familiarize practitioners with this issue for the purposes of improved risk analysis, prevention, detection, and treatment of perpetrators, as well as the legal implications that arise. Because neonaticide, the intentional killing of a child less than one day old, presents unique risk factors compared with infanticide, this topic is also reviewed.

**Infanticide**

**Victims**

As with other violent acts, risk analysis of infanticide could provide a means of prevention. Foremost among risk factors for infanticide is a history of previous abuse (4). In a study of infanticides in the United States, Fujiwara et al. (5) found that 39 of 71 cases of infanticide had evidence of previous physical abuse. Furthermore, fatal abuse has been noted to occur in “young, unwanted children” (6). Infant sex is also a risk factor for homicide. Evidence suggests that male infants are more likely to be victims of infanticides in Western cultures (5). However, female infanticide is a more common practice in Asian cultures, potentially secondary to “son preference,” and critics of the one-child policy in China suggest that the additional pressures of population control may lead to additional cases of homicide (1).

Infant age also contributes to the risk for homicide. Of Japanese murder victims under the age of 15 years, children under 1 year are at the greatest risk (7). Overpeck et al. (8) examined the murders of 2,776 infants in the United States and found that 5% of homicides occurred on the first day of life, 25% by 2 months of age, 50% by 4 months of age, and 66% by 6 months of age.

**Perpetrators**

Describing perpetrators of infanticide could also prove invaluable to risk assessment. Children are more likely to be killed by their caretaker than a stranger (5). In the aforementioned landmark analysis of infanticide risk factors in the United States, Overpeck et al. found that young, multiparous mothers were more likely to commit infanticide than other parents, and the authors also reported the following additional risk factors: maternal age <19 years, maternal education <12 years (confounded by age), unmarried, African American or American Indian race, first prenatal visit after 6 months gestation or no prenatal care, and gestational age <28 weeks at delivery (8). However, these findings do not separate neonaticide from infanticide, and other studies show that mothers who commit infanticide tend to be married or living with their partner, >25 years old, and suffer from psychopathology (9).

Similarly, a review of child homicides occurring between 1995 and 2005 in Austria and Finland found that 51% of child homicides committed by mothers were infant victims, compared with a rate of 7% of infant victims by paternal perpetrators (10). Compared with fathers, mothers were less likely to have a history of violent offenses, were more likely to conceal their crimes, and were more likely to use drowning, negligence, and poisoning as methods (10). In a sample of 110 Italian women who committed infanticide, Ciani et al. (11) found that mothers who committed infanticide were more likely to have had psychopathology (most commonly major depressive disorder of those pathologies that could be identified), to have engaged in violent killing of the infant, to have committed or attempted suicide after the homicide, and to have made no attempt to conceal the bodies of the infants. While most women who commit infanticide do not suffer from postpartum psychosis, the incidence of suicide or infanticide among women with this psychopathology nears 5% (12).

Fathers who commit child homicides are more likely to kill older children than infants (10, 13). In an analysis of fathers who commit child homicides, researchers found that only 20% of the 458 child homicide victims were infants (excluding neonates), and only 1.5% of the victims were neonates (13). Research indicates that fathers who commit infanticide are more likely to cause shaking/beating injuries, and the infant is more likely to be taken to the hospital (5).

The risk of infanticide in families including adopted and step children is still debated (14, 15). While there may or may not be a relationship between blended families and infanticide risk, step parents do commit these crimes. Murders by step parents are more likely to involve anger, rage, ongoing abuse, and death by beating rather than use of a weapon, drowning, or poison (16). Other factors that may increase the risk of committing infanticide include increased rates of economic stress (4, 17) and inter-actional problems between parents (17).

**Neonaticide**

The intentional killing of an infant less than 1 day old, or neonaticide, appears to have different risk factors for the vic-
The incidence of neonaticide is equal among male and female neonates (6), unlike the incidence of infanticide. Mothers who commit neonaticide tend to present in a different fashion. Putkonen et al. (10) found that mothers were more likely to commit neonaticide than fathers. Ciani et al. (11) reported that mothers who committed neonaticide were without psychopathology, young, single, poor, used nonviolent means (such as abandonment), and attempted to conceal the bodies. Similarly, a series of 32 documented neonaticides describes mothers as having no psychopathology and seeking little to no prenatal care and concealing or even denying the existence of the pregnancy (18).

**Legal Considerations**

Currently in the United States, parents who kill their infants are able to plead not guilty by reason of insanity, and there is no special consideration for postpartum status. However, some have argued that this should be the case, given the prevalence of postpartum mental illness (19). Arguments against infanticide statutes include a focus on redundancy if insanity defense standards already exist, inherent gender bias, diminished value of infant life, and the fact that maternal mental illness continues after a child reaches 1 year of age (20). It is recommended that practitioners familiarize themselves with the mental health laws in their state.

**Risk Assessment and Prevention**

Having considered the epidemiology and risk factors of infanticide, one key question remains: How can clinicians help prevent infanticides? Primarily, a comprehensive risk assessment for potential harm to the infant should be performed. Some suggest that clinicians should perform in-depth risk assessments when evaluating patients, similar to a suicide risk assessment, and it has been shown that during risk assessments, practitioners are more likely to ask about general homicidal thoughts rather than specific harm to children (4). Friedman and Resnick (4) suggested direct questioning about thoughts, plans, and intent to harm children, with low thresholds for hospitalization of mothers contemplating harm (4). Similarly, clinicians should be wary of warning signs in mothers and fathers, including depressive symptoms, suicidal thoughts, feelings of insufficiency, relationship strain, and history of abusing children (17). Additionally, history of mental illness, domestic violence, significant infant illness, and lack of prenatal treatment should be added to this list of red flags.

Another aspect of the prevention of infanticide lies with the practitioner’s ability to adequately treat any modifiable risk factors. For example, treatment of underlying mental illness could help reduce the risk of infanticide. Examples of treatment include couples counseling, hospitalization, referral to domestic violence support groups, and close follow-up. Finally, referral to the Department of Human Services for suspected child abuse is not only recommended but mandatory.
in many jurisdictions. Characteristics of perpetrators and victims and risk assessment and prevention strategies are summarized in Table 1.

Summary

The killing of infants, sometimes thought to be a problem of the ancient world, is still practiced across the globe today. Multiple studies have investigated the various risk factors in the infant and perpetrator, which can be used to perform risk assessments. Mental health professionals are often asked to perform risk assessments for violence, including risk of infanticide and neonaticide. It is important for consultants to consider the age of the child when assessing the risk of homicide, as differences between the possible perpetrators exist. Because of the legal implications of this issue, practitioners should familiarize themselves with the legal statutes governing their jurisdictions. Using these suggested strategies for risk assessment, prevention could inform the treatment of possible perpetrators and prevention of homicides.

Dr. House is a fourth-year resident in the Department of Psychiatry, University of Arkansas for Medical Sciences, Little Rock, Ark.

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References

Test Your Knowledge Has Moved

Our Test Your Knowledge feature, in preparation for the PRITE and ABPN Board examinations, has moved to our Twitter (www.twitter.com/AJP_ResJournal) and Facebook (www.facebook.com/AJPRResidentsJournal) pages.

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Submissions should include the following:
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*Please direct all inquiries to Rajiv Radhakrishnan, M.B.B.S., M.D., Senior Deputy Editor (rajiv.radhakrishnan@yale.edu).
Residents’ Resources

We would like to welcome all our readers to this new feature of the Journal! Here we hope to highlight upcoming national opportunities for medical students and trainees to be recognized for their hard work, dedication, and scholarship.

*To contribute to the Residents’ Resources feature, contact Tobias Wasser, M.D., Deputy Editor (tobias.wasser@yale.edu).

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<tr>
<td>Rappeport Fellowship</td>
<td>American Academy of Psychiatry and the Law (AAPL)</td>
<td>The fellowship offers an opportunity for outstanding residents with interests in psychiatry and the law to develop their knowledge and skills. Fellows will attend the Annual Meeting of AAPL and AAPL’s annual Forensic Psychiatry Review Course, which precedes the meeting.</td>
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<td>ACNP</td>
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<td>Offers a stipend for child and adolescent psychiatry residents and junior faculty who have an interest in beginning a career in child and adolescent mental health research. By providing one award to a child and adolescent psychiatry junior faculty member or resident for pilot research on learning disabilities, we support a young investigator at a critical stage, encouraging a future career in child and adolescent psychiatry research.</td>
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