Consensus Statement and Research Needs

The Role of Dopamine and Norepinephrine in Depression and Antidepressant Treatment

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During a special session, the faculty identified several specific areas related to the role of dopamine and norepinephrine in depression and antidepressant treatment that either warrant the clinician's attention or are in need of more research. Areas of interest include fatigue and lethargy in depression, treatment strategies for treatment-resistant depression, the somatic presentation of depression, neurobiology of fatigue and its role in determining treatment, symptom rating scales, and sexual side effects. In addition, the faculty discussed the importance of patient psychoeducation and self-management as well as the ways in which disease models of depression affect treatment.

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The faculty held a special session to achieve a consensus regarding the role of dopamine and norepinephrine in depression and its treatment. Their task was to identify points deserving of emphasis as well as topics in need of more research and study.

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FATIGUE AND HYPERSOMNIA

Fatigue and hypersomnia are symptoms that feature prominently in depression. Fatigue has a lifetime prevalence in the community of about 13%, and has been shown to increase the risk of depression 28-fold.[1] Although, in the last 20 or 30 years, depression has been conceptualized as being a mental state with feelings of worthlessness and guilt, earlier views of depression involving prominent lethargy and fatigue were more common. In fact, the results of several studies suggest fatigue to be approximately as common a complaint among depressed outpatients as depressed mood itself.[2,3] Therefore, focusing on fatigue and hypersomnia in depression may be helpful in optimizing the definition and diagnostic criteria of depression.

The presence of fatigue and hypersomnia may also help direct the treatment of depression. Although the selective serotonin reuptake inhibitors (SSRIs) can be successful in helping alleviate depression in many instances, they can often leave patients with residual symptoms of fatigue and excessive sleepiness.[4] Therefore, developing pharmacotherapeutic strategies that are more successful in resolving fatigue and hypersomnia may further improve the standard of care for patients with depression. For example, preliminary evidence suggests that the treatment of major depressive disorder (MDD) with antidepressants that inhibit the reuptake of both norepinephrine and dopamine may result

in lower rates of residual fatigue and hypersomnia than SSRI treatment.[5] This finding, however, has yet to be demonstrated prospectively with the use of double-blind, placebo- and active-comparator controlled trials involving the use of clinician- and patient-rated scales specifically designed to measure fatigue and hypersomnia. In addition, it should also be pointed out that a recent study has failed to find a difference in the degree of resolution of fatigue among MDD patients treated with an SSRI or the norepinephrine-selective reuptake inhibitor reboxetine.[6] Finally, there are no studies comparing the degree of resolution in fatigue or hypersomnia in MDD patients treated with either an SSRI or a serotonin-norepinephrine reuptake inhibitor (SNRI).

TREATMENT-RESISTANT DEPRESSION

Treatment-resistant depression is still an area of uncertainty; clear definition and treatment guidelines do not yet exist. A large European trial will soon begin to produce usable data, but at present, there are no systematic, quality data that could help in this area.

One treatment option that could have some utility is starting with 2 drugs simultaneously at the beginning of therapy, when past resistance to treatment is well documented. However, few studies have systematically examined that option and certainly none have done so in a multicenter fashion. Another treatment option in need of more research is switching within or between drug classes. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial considers depression to be a chronic illness with frequent comorbidity and is yielding helpful data on how to develop a treatment plan for patients with treatment-resistant depression.[7,8]

Future developments in depression such as pharmacogenetics and perhaps more predictive symptomatology may help determine more targeted treatments that can be given at the start of therapy and that will minimize the risk of treatment resistance.

SOMATIC PRESENTATIONS OF DEPRESSION

The somatic presentations of depression vary in different cultures, although there is a degree of overlap, and patients benefit from the treatment of both somatic and psychological symptoms. In addition, a view of somatic symptoms as masking depression and preventing it from being diagnosed is of limited utility; somatization exists, but it is not the sole explanation as to why depressive symptoms are not recognized. Another factor to consider when assessing a patient who reports somatic symptoms is whether those symptoms are drug side effects, of either an antidepressant or another medication or herbal remedy the patient is taking.

NEUROBIOLOGY

It may be possible to construct a systematic conceptualization of the different brain regions and neurotransmitters that may be involved in the different types of depressive symptoms such as lethargy and fatigue, which include not only motor retardation but also slowing and failure of memory, attention, and concentration.[9] One area that bears more research is the role of dopamine in these symptoms, since when normal volunteers take D_2 blockers, they can develop a range of symptoms such as inattention, blunted emotions, clouded memory, and, sometimes, motor dysfunctions, such as akathisia. There is also growing evidence in Parkinson's disease that subcortical dopaminergic dysfunction may lead to symptoms such as depression and cognitive slowing, in addition to motor impairments.[10]

SYMPTOM RATING SCALES

The faculty agreed that better symptom rating scales are needed for the assessment of fatigue in depression. There is evidence that the self-report Inventory of Depressive Symptomatology scale (IDS) may be better than some of the other available rating scales because it is targeted at the whole range of symptoms.[11] Ideally, the IDS could be used in future studies so its results could be compared with those of the Hamilton Rating Scale for Depression, which clearly contains gaps in terms of examining all elements of mental changes in depression and focuses too heavily on somatic symptoms.

SEXUAL SIDE EFFECTS

An important point to emphasize is that psychotropic drugs are not the only medications that cause sexual side effects—more than 100 other drugs have been recognized as possibly causing these problems as well.[12] In addition, sexual dysfunction can be caused by concomitant physical disorders and concomitant abuse of alcohol and other drugs. Therefore, many of the sexual side effects that a patient with depression might experience could be misattributed to antidepressant treatment. Spontaneous reports of sexual side effects are infrequent, but if patients with depression are asked about sexual dysfunction, a large number will confirm that they have experienced some type of dysfunction and report that it does not necessarily go away with treatment. In fact, sexual side effects may worsen as treatment continues, as a recent study has shown.[13]

Unfortunately, there are few credible options for treating antidepressant-induced sexual side effects. Tolerance develops in as few as 5% to 10% of patients. For example, in a descriptive study[14] of 344 patients treated with SSRIs, 200 (58.14%) reported sexual side effects. Of those, 156 were available at 4- to 6-month follow-up. In only 9

(5.8%) of 156 did dysfunction resolve completely during drug therapy; 81.4% (127 of 156) experienced no improvement. Drug holidays are typically ineffective, except against orgasm and ejaculatory problems, and raise the risk of relapse or recurrence, so antidotes or changing antidepressants may be the most effective options for erectile problems. Phosphodiesterase inhibitors such as sildenafil have some value, particularly in men, but not in women. In addition, there is some evidence that dopaminergic agents as add-ons might be of utility.

The faculty encourages doctors to consider using research scales, such as the Changes in Sexual Functioning Questionnaire (CSFQ), Arizona Sexual Experiences Scale (ASEX), or Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ) in their clinical practice. It should be stressed that other pharmacologic treatments, such as with the antipsychotics, can cause sexual side effects as well, and some of them, particularly the more potent D_2 blockers that increase prolactin levels (e.g., risperidone), are more problematic than others (such as quetiapine[15]). This fact supports the view that the dopamine system is likely to be implicated in sexual function. For more information on the management of sexual dysfunction, see Hatzichristou et al.[16]

THE PATIENT'S PERSPECTIVE: PROMOTING SELF-MANAGEMENT

Several key issues from the patient's perspective need to be addressed for depression treatment to be successful. It is useful for patients to have a confidant who can play a part in their treatment, to help patients access their feelings. This idea contradicts the assumption that many clinicians make, that patients will be embarrassed to talk about their depression in front of those closest to them. Having a supporter present can actually increase the patient's level of comfort with treatment. Compliance is also a complex issue. The building of a therapeutic liaison and patient education, rather than simply providing information, are critical to improving adherence.

Challenges in the treatment of depression include both an aging population, with substantial physical comorbidity, and the changing expectations of a younger population that relies on the Internet for medical information. Also, this population of young people may have a higher incidence of diagnosed depression than past generations, and the overall level of depression may therefore increase as this generation ages.

The faculty agreed that patients need to be empowered to participate in their own treatment. The paternalistic view of the doctor-patient relationship, in which the doctor manages a passive patient, is outdated, and patients have been shown to benefit from self-management of their disorder through psychoeducation about the disease and specific effects of the disease within themselves as well as the use of cognitive-behavioral therapy (CBT) self-help material.[17] When patients feel involved in the management of their depression, they will very likely be more personally invested in their treatment regimen and will be more likely to adhere to treatment.

FROM "MOOD SWING" TO ILLNESS: REFRAMING DEPRESSION

The attempt to frame depression as not merely a "mood swing" but as an illness that is often chronic and relapsing has been ongoing and needs to continue. It may be that the only way an illness model of depression will fully take hold—at least for moderate and severe depression—is when it can be defined in terms of its underlying neurobiology. Trying to "normalize" a patient's feelings may minimize the chance that the patient will tell his or her doctor what the problems really are; there is an opportunity for effective health education programs. Health education programs cannot only help allay some of the stigma associated with depression but can also help the public understand that medication treatment is effective and nonaddictive and often needs to be taken long term.

Treatment guidelines can be helpful, but the faculty expressed concern that, in some, treatment approaches are recommended on the basis of a low level of evidence instead of from multicenter, placebo-controlled trials. In addition, not all treatment guidelines take into account the costs and practicality of some recommendations—CBT, for example, can certainly be effective, but it may be difficult for a patient to find or pay for such treatment.

RESEARCH NEEDS

The faculty identified several areas that are deserving of more research and study. They included the following:

- The evidence for the role of dopamine and norepinephrine in depression is based on a number of different sources, drugs effects, and intervention studies, but their role needs more research before findings can be considered conclusive.
- Smoking may affect dopamine and norepinephrine; more research is needed regarding antidepressant treatment in smokers and those who are trying to stop smoking.
- Although preliminary studies suggest that norepinephrine/dopamine reuptake inhibitors are more effective than the SSRIs in treating fatigue and hypersomnia in depression, more systematic study, including clinical trials specifically designed to measure changes in fatigue and hypersomnia in depression, is needed.
- Residual fatigue and hypersomnia may have a high predictive power in terms of relapse if anti-

depressant treatment is stopped; future research is needed.

- It is unclear whether "mild" depression should be diagnosed as full-fledged depression; more research is needed to clarify diagnostic criteria and treatment standards and whether severity of depression at presentation to the physician affects response to treatment and outcome.
- Additional study is needed on the culture-specific presentation of depressive symptoms.

Drug names: quetiapine (Seroquel), risperidone (Risperdal), sildenafil (Viagra).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this activity.

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