Letters to the Editor

Agitation and Inpatient Suicide

Sir: I read with interest the excellent article by Busch and colleagues[1] describing the clinical correlates of suicide among hospitalized patients. It is argued that the presence of severe anxiety and agitation symptoms may be an important but treatable acute predictor of suicide. While aggressive pharmacologic treatment of suicide-related target symptoms is advisable, it is important to determine the context and pattern of evolution of such symptoms in the course of psychiatric illness, particularly mood disorders.

The results of this study[1] demonstrated evidence of significant psychic anxiety or agitation in nearly 80% of patients during the week prior to suicide, but only 8% (N = 6 of 76) of the cases were diagnosed with agitated depression at admission. It is not clear whether symptoms of psychic anxiety and agitation were present in variable degrees during the entire index hospitalization or a change in psychomotor activity occurred proximally to the time of suicide. Another issue that needs clarification is the source of these symptoms that can occur in relation to symptomatic or syndromal comorbidity with anxiety. The use of antidepressants in patients with a bipolar diathesis can lead to the development of agitation and insomnia against the backdrop of atypical symptoms such as psychomotor retardation and hypersomnia. Finally, mixed episodes that are associated with a high risk of suicide are often accompanied by symptoms including anxiety and agitation.

Contrary to the results of studies showing that the diagnosis of bipolar disorder, particularly bipolar II disorder, is associated with an elevated risk of suicide, the number of individuals with bipolar disorder in this study was surprisingly low.[2,3] The rapidly fluctuating clinical course and the presence of symptoms including mood lability and psychosis in some patients raises the possibility of a higher than reported prevalence of bipolarity, particularly mixed episodes.

As antidepressants can cause mood instability in some patients, it is important to study the relationship between changes in the clinical state, especially cognition, mood, psychomotor activity and sleep, and the use of these drugs. If case-controlled studies confirm such an association, caution may be needed regarding the use of antidepressants in at least some patients at acute risk for suicide.

Dr. Sharma reports no financial or other support of this letter.

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Verinder Sharma, M.B., B.S., F.R.C.P.C.
Regional Mental Health Care
London, Ontario, Canada

Dr. Busch and Colleagues Reply

Sir: We appreciate the thoughtful questions raised by Dr. Sharma concerning the findings reported in "Clinical Correlates of Inpatient Suicide." He questions our finding that 50% of the patients showed recorded evidence of agitation and 67% showed recorded evidence of severe psychic anxiety in the week before suicide, while only 8% were admitted with the diagnosis of agitated depression. It is important, in addressing this question, to keep in mind that the records reviewed originated from community and state hospitals in 71% of the cases and contained clinical rather than research diagnoses. The cases were hospitalized over a period spanning different generations of DSM classifications. A further review of cases for this letter revealed that few of the highly anxious or agitated patients received a diagnosis of agitated depression on admission. It was our impression, based on the low rate of prescription of anxiolytic or antipsychotic medications, that although severe anxiety and agitation were described in the records, little attention was given to these presentations.

We are now reviewing earlier records in the index admissions (33 of the patients died during the first week of hospitalization), as well as prior admissions where available (for 36 of the patients this was their first hospitalization), to investigate the important question of whether the severe anxiety/agitation was present at admission or during prior admissions or whether it evolved acutely in individual patients. We will report those findings when we complete this review.

With regard to the observation that the use of antidepressants might aggravate or initiate mixed states with agitation in undiagnosed bipolar patients (it was noted that the number of primary bipolar diagnoses in the group was surprisingly low), we reviewed secondary diagnoses in the series for evidence that cases might be in the bipolar spectrum and for the use of antidepressant medications in these cases. A total of 5 cases were given a diagnosis of bipolar disorder or rule-out bipolar disorder. Of these, 2 cases had been given any antidepressant medication. We found that 18 additional cases may have had symptoms associated with the bipolar spectrum, including diagnoses given and rule-out diagnoses (schizoaffective, N = 5; atypical psychosis, N = 2; diagnosed recurrent unipolar depression, N = 10; and rule-out affective illness, N = 1), and 12 of these 18 had received antidepressants in the hospital. The overall incidence of antidepressant treatment in the entire sample was only 51%, and the dosages given were, in general, quite low. Even though antidepressants may have been associated with agitation on a temporal basis, it is not possible to draw any conclusions about causality.

We agree that these are important questions but remain impressed at the low incidence of cases in which either severe agitation or severe psychic anxiety was recognized to the extent that attempts were made to address these symptoms with specific treatment in this sample of inpatient suicide cases. As with the antidepressants, the use of anxiolytic medications

was quite low; only 42% (32/76) received any daytime anxiolytic medications.

Again, we appreciate Dr. Sharma's incisive questions.

Dr. Fawcett has received honoraria from and serves as a consultant to and on the speakers/advisory boards for Abbott and Eli Lilly. Drs. Busch and Jacobs report no financial or other support of this letter.

Katie A. Busch, M.D.
Rush Medical College
Chicago, Illinois
Jan Fawcett, M.D.
University of New Mexico School of Medicine
Albuquerque, New Mexico
Douglas G. Jacobs, M.D.
Harvard Medical School
Cambridge, Massachusetts

Treatment of Anxiety in Suicidal Patients

Sir: The report by Busch et al.[1] confirms 2 points about suicide that most clinicians, risk managers, and legal consultants have known for some time. First, it only takes seconds to kill yourself. Second, a person who really wants to do it would be unlikely to tell anyone at the time. This report provides a powerful reminder for hospitals and clinicians who may still be using inadequate observation procedures (e.g., q 15-minute checks) for inpatients. The futility of so-called no-suicide contracts for preventing suicide has also been demonstrated.[2] The treatment implications of the article and of the commentary by Goodwin[3] are either unclear or doubtful, however. We infer that the recommendation is for treatment of anxiety in suicidal patients with sedative/hypnotics. If this is not the recommendation, we think it should be clarified.

The occurrence of anxiety as a common symptom of just about every mental as well as other medical disorder is well known. Data suggest that severe anxiety in depressed patients may be one of several factors correlated with eventual suicide.[4] We are unaware, however, of any data supporting a conclusion that "aggressive treatment of severe anxiety symptoms"[1(p19)] has a positive effect on preventing suicide. Likewise, we know of no scientific validation that "aggressive pharmacologic management of anxiety, panic, and insomnia should work."[3(p13)] It cannot be assumed that the symptomatic treatment of anxiety will lower the risk for suicide. The opposite might be true as well; for example, what if the anxiety is the last barrier blocking the suicidal act? The phenomenon of disinhibition resulting from sedative/hypnotics (including alcohol) is of serious concern in such a scenario.

Experienced psychiatrists have told us that they commonly prescribe sedative/hypnotics to anxious, depressed inpatients and none have committed suicide. We regard these observations as true. Suicide is a rare event under any circumstances, however, so these negative observations are of very little statistical or clinical significance. The hazard of dependency on sedative/hypnotics goes without saying. In our experience, though, it is often forgotten by physicians that these compounds can also be depressogenic.[5,6] The high frequency of use of intoxicating, abusable substances found in blood toxicology screens of those who commit suicide is well documented.[7–9] Although the role played by these substances in the causation of suicides cannot be determined, logic says that the use of such medications (or alcohol) by someone who is depressed (and thus potentially suicidal) should be considered contraindicated. These hazards may not be present for non–central nervous system depressant anxiolytics (e.g., buspirone, hydroxyzine). Nonetheless, "the question of whether aggressive treatment of this symptomatology, if properly assessed and recognized, could reduce suicide"[1(p18)] remains unresolved. We disagree strongly with the statement, "The presumed cause of the symptom may be less important than its presence and severity for this purpose."[1(p18)] Clinical wisdom tells us not to cover up important symptoms in lieu of definitive diagnosis and treatment. Systematic clinical investigations of suicides give strong evidence that depression plays a fundamental role in suicide.[10] Compelling data indicate that aggressive treatment of depression does correlate positively with reduced suicides.[11]

Until convinced to the contrary by suitable data, we conclude that intoxicating, abusable medications should be avoided for depressed patients. In our opinion, the best thing to do about the occurrence of anxiety with depression is to treat the depression aggressively. We believe this is the best medical approach to suicide prevention.

The authors report no financial affiliation or other relationship relevant to the subject matter of this letter.

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Charles L. Rich, M.D.
University of South Alabama
Mobile, Alabama
Göran Isacsson, M.D., Ph.D.
Karolinska Institute
Huddinge, Sweden

Drs. Fawcett, Busch, and Jacobs Reply

Sir: We appreciate the opportunity to respond to the questions and objections raised by Drs. Rich and Isacsson. They correctly point out that there are no data proving that aggressive treatment of severe anxiety symptoms or aggressive pharmacologic management of anxiety, panic, and insomnia prevents

suicide. Our assertion is based on repeated findings[1–3] that these symptoms, in severe form, appear to be present in depressed patients shortly prior to suicide or serious attempts. These findings suggest to us that rapid treatment will reduce the risk of suicide even before the positive effects on depression of antidepressant medications occur. We welcome any advice on the design of an ethical study to prove this assertion directly. It seems logical to us (our clinical experience notwithstanding) that if severe psychic anxiety, panic attacks, and global insomnia differentiate suicides from non-suicides among severely depressed patients from a week to a year, whereas expressed suicidal ideation, prior suicidal ideation, and hopelessness do not separate them acutely but only at 2- to 10-year follow-up,[1] then one might consider treatment of anxiety, panic, and insomnia symptoms to reduce the likelihood of suicide.

We agree with the observation that anxiety is a common symptom; it was found present in moderate severity in up to 70% of patients with major depression on the basis of the Schedule for Affective Disorders and Schizophrenia-current (SADS-C).[4] We are referring to severe psychic anxiety as rated on the SADS-C (a score of 5 or above), which requires a clinical determination based on the intensity of the experienced anxiety as well as its duration throughout the patient's day.

Clonazepam (not a sedative hypnotic but a long-acting anxiolytic-anticonvulsant), as an adjunct to antidepressant treatment, has been shown to result in a more rapid response to antidepressant medications,[5–7] and we think that the risk associated with short-term use of benzodiazepines is much less than the risk of suicide, with a caveat for the use of alprazolam in borderline personality disorder patients.[8] Other agents have been used more recently, such as atypical antipsychotic medications that block 5-HT_2 receptors and divalproex,[9–12] especially in agitated, anxious patients, including patients with bipolar mixed states. The main point we believe our studies[1,3] illustrate is that some patients evidence modifiable severe anxiety symptoms that are associated with suicide. Aggressive treatment of these symptoms may reduce suicide. The pharmacologic treatment (adequate doses of benzodiazepines, atypical antipsychotics, or divalproex) should be added to antidepressants, given the known delay of action of antidepressants and possible failure in producing therapeutic benefit.

We agree that aggressive treatment of depression is important for prevention of suicide, but believe the literature indicates that antisuicide effects of antidepressant medications do not come into play in the short term (perhaps not for 6 months). Khan's analysis of data in the U.S. Food and Drug Administration database on selective serotonin reuptake inhibitor (SSRI) treatment of depression and anxiety disorders showed no antisuicide effects compared with placebo treatment in 8-week studies.[13] Rich and Isacsson's citation of their work[14,15] suggesting that the use of SSRI drugs reduces suicide shows a correlation of increasing rates of SSRI use with decreasing suicide rates but does not make the claim that suicide rates of patients with affective disorders are reduced to the rates of the normal population. In our view, the strongest evidence available that treatment prevents suicide in high-risk patients is Angst and colleagues' observation over a 35- to 38-year follow-up of a 2.5-times reduction in suicide in patients hospitalized for a major affective disorder who had received at least 6 continuous months of treatment with antidepressants, antipsychotics, and lithium, despite their having more severe symptoms than those who received less than 6 months of continuous treatment.[16] We agree that depression should not be undertreated with antidepressants, which is all too common.[16]

We believe that our data lead us to the conclusion that antidepressant treatment alone is not enough in patients manifesting severe psychic anxiety, agitation, panic attacks, and severe insomnia and that alcohol use in these situations suggests a tragically ineffective and harmful attempt at self-treatment of these symptoms. We feel that the sustained, but short-term, use of rapid, long-acting, anxiolytic medications may reduce the likelihood of suicide in these patients and would like to perform a definitive study to test this, but until that can be accomplished, we advocate the detection of acute risk factors and their aggressive treatment in patients.

Dr. Fawcett has received honoraria from and serves as a consultant to and on the speakers/advisory boards for Abbott and Lilly. Drs. Busch and Jacobs report no financial affiliation or other relationship relevant to the subject matter of this letter.

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Jan Fawcett, M.D.
University of New Mexico School of Medicine
Albuquerque, New Mexico
Katie A. Busch, M.D.
Rush Medical College
Chicago, Illinois
Douglas G. Jacobs, M.D.
Harvard Medical School
Cambridge, Massachusetts

Effectiveness of Close Watch Precautions in Suicidal Patients

Sir: In commenting on the article on suicide by Busch et al.,[1] Frederick K. Goodwin, M.D.,[2] is shocked and surprised to find that the "time-honored routine inpatient procedure—15-minute checks—fell tragically short"[2(p13)] in preventing suicide. The frequent failure of such a logical procedure to accomplish its mission may be explained in part by its secondary function as a self-fulfilling prophecy: the appearance of the nurse's eye behind the window in the door 4 times an hour is a regular reminder that the patient is *expected* to have found a way to death. This persistent and pessimistic message serves to counteract whatever message of hopefulness the hospital's program otherwise delivers.

The significance of this double message was dramatically illustrated some years ago when a patient in a West Coast psychiatric hospital killed himself. The hospital, previously noted for its openness, responded by increasing patient controls, and as further suicides and suicide attempts occurred, the hospital became more and more rigid and apprehensive until it was eventually forced to close.[3,4]

There may be a similar reason for the relative ineffectiveness of the no-suicide contract (Busch et al.[1] found that 28% of patients who committed suicide had such a contract). Staff on a ward are likely to check on all patients, with or without contracts, and so signal an expectation that the contracted patients will not abide by the contract. For legal as well as practical reasons, suicidal patients have to be checked on; the question is, how can it be done with the least amount of dissipation of the atmosphere of hope that is so essential to cure?

Dr. Aldrich reports no financial affiliation or other relationship relevant to the subject matter of this letter.

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C. Knight Aldrich, M.D.
University of Virginia School of Medicine
Charlottesville, Virginia

Drs. Fawcett, Busch, and Jacobs Reply

Sir: The issue raised by Dr. Aldrich is particularly interesting because there seem to be few data addressing the question of how patients actually perceive close watch precautions. His comment highlights an area that in our opinion would require empirical data to understand. We were unable to find any peer-reviewed article dealing with this issue in the MEDLINE database. How do patients feel about and respond to suicide precautions or close watch? Do they feel more hopeless or better cared for? Dr. Aldrich suggests that suicide precautions create a "self-fulfilling prophecy," referring to "the appearance of the nurse's eye behind the window in the door 4 times an hour."

One of the authors' (J.F.'s) experience in over 35 years of inpatient practice leads to the belief that patients can feel reassured and cared for by close watch precautions, and we do not agree that they deepen hopelessness. We call 15-minute checks "close watch" because they are certainly not effective in preventing a determined patient from preventing suicide. These checks, when ordered, are not intended to be accomplished through an "eye behind the window," but through frequent positive, supportive staff-patient interactions. The question of induced pessimism versus support could easily be studied in an acute inpatient setting, and then assumptions about the issue could be built on data. It should be noted that the vast majority of patients on close watch precautions do not commit suicide, a fact that lends no empirical support to Dr. Aldrich's assertions.

The point of our article is that patients at high suicide risk feel that their situation is hopeless with or without precautions and often do not convey their intent, which would invite help. Some depressed patients are perhaps past the point of responding to the reassurance of close watch precautions or a "no-harm contract" unless their psychic pain is relieved. Humane clinical care demands that we strive to identify these high-risk patients. On the basis of the data reviewed and presented,[1] we suggest that one way to potentially reduce suicide is to recognize and aggressively treat severe anxiety and agitation with rapidly effective pharmacotherapy until these patients' depression can be successfully treated. This suggestion is based on our finding of severe anxiety/agitation in many patients (79%) during the week prior to their suicide.[1]

Dr. Fawcett has received honoraria from and serves as a consultant to and on the speakers/advisory boards for Abbott and Lilly. Drs. Busch and Jacobs report no financial affiliation or other relationship relevant to the subject matter of this letter.

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Jan Fawcett, M.D.
University of New Mexico School of Medicine
Albuquerque, New Mexico
Katie A. Busch, M.D.
Rush Medical College
Chicago, Illinois
Douglas G. Jacobs, M.D.
Harvard Medical School
Cambridge, Massachusetts

Two Cases of Quetiapine Augmentation for Donepezil-Refractory Visual Hallucinations in Dementia With Lewy Bodies

Sir: Dementia with Lewy bodies (DLB) is the second most common form of dementia following Alzheimer's disease. DLB is characterized clinically by 3 symptoms: progressive cognitive decline with daily fluctuations, visual hallucinations, and parkinsonism.[1] DLB is associated with substantial cortical cholinergic deficiency that presumably reflects selective loss of cholinergic inputs from the basal forebrain cholinergic nuclei.[2]

The focus of pharmacologic therapy for DLB involves the above triad of symptoms. Recently, several studies have shown that cholinesterase inhibitors are effective in treating not only cognition but also visual hallucinations.[3–6] Nonetheless, a significant proportion of DLB patients' hallucinations do not respond to cholinesterase monotherapy. Although the typical

approach to treating visual hallucinations has been to administer a drug with dopamine-blocking properties,[7] DLB patients may be exquisitely sensitive to antipsychotic agents, particularly conventional neuroleptics. Several investigators have reported that both typical[8] and atypical antipsychotics such as risperidone[9] and olanzapine[10] induce serious side effects particularly in DLB.

This report describes 2 cases of DLB in which visual hallucinations gradually became refractory to donepezil but were responsive to quetiapine addition. This report is, to our knowledge, the first showing a therapeutic effect of quetiapine augmentation in patients with these particular characteristics.

Case 1. Ms. A, a 75-year-old woman, was clinically diagnosed as suffering from DLB. Treatment with 3 mg/day of donepezil was started, and soon after, her visual hallucinations clearly diminished and her dose of donepezil was increased to 5 mg/day. Although her visual hallucinations abated for 4 months, her hallucinations gradually reappeared and became more severe. She saw images of a naked woman with a blue cap lying beside her husband, some ratlike insects wandering on the wall, her dead mother and father, a mermaid, a butterfly, and children in her house. Although her donepezil dose was increased to 10 mg/day, there was no effect, and the dose was reduced to 5 mg/day.

Ms. A was then admitted to our university hospital in June 2002. Quetiapine treatment was started and gradually increased from 25 to 150 mg/day and was combined with 5 mg/day of donepezil. Initially, the patient was in a confused state, but her condition slowly stabilized. In this instance, quetiapine had brought on orthostatic hypotension, for which the patient received midodrine.

Three weeks after admission, Ms. A's visual hallucinations decreased. Two months later, the patient was discharged on treatment with 5 mg/day of donepezil and 150 mg/day of quetiapine. During the subsequent 8 months, her visual hallucinations almost completely remitted. At present, treatment with quetiapine in combination with donepezil has been successful for 10 months.

Case 2. Mr. B, a 76-year-old man, was clinically diagnosed as suffering from DLB. When given the opportunity to discuss his hallucinatory experiences openly, he described vivid images appearing in his bedroom every night of people drinking and eating, ladies dancing, children sleeping, dwarfs shooting water at him, and Spider-Man shooting a net at him. None of them spoke, but the dwarf images interrupted his going to the toilet. Treatment with 3 mg/day of donepezil was initiated in April 2001, and after starting donepezil, the patient did not see hallucinatory phenomena (for 2 of 7 nights) for the first time in recent years.

Mr. B's donepezil dose was increased to 5 mg/day, and he reported no further visual hallucinations for 10 of 14 days. However, he complained of severe general fatigue and developed signs of parkinsonism in the form of a gait disturbance. As such, levodopa was added to the 5-mg/day dose of donepezil, and 2 months later, the donepezil dose was increased to 10 mg/day.

Since the effect of donepezil on visual hallucinations was attenuated with time, 25 mg/day of quetiapine was added to 10 mg/day of donepezil and 100 mg/day of levodopa. Thereafter, the quetiapine dose was gradually increased to 200 mg/day over the course of 4 months, leading to a gradual decrease in frequency and intensity of visual hallucinations. At the patient's request, quetiapine was subsequently withdrawn over $1^1/_2$ months. Two weeks later, the visual hallucinations were recurring every night. In response, 200 mg/day of quetiapine was resumed in addition to 10 mg/day of donepezil and 150 mg/day of levodopa. Once again, the visual hallucinations decreased; however, in response to further complaints of fatigue, Mr. B's quetiapine dose was reduced to 100 mg/day with the addition of 0.25 mg/day of cabergoline.

Mr. B's visual hallucinations decreased and became fleeting during the following year. Interestingly, his wife volunteered, "Recently, my husband has rarely shaken a stick in the bedroom," suggesting that he was no longer bothered by the visual hallucinations. At the present time, the combined regimen of quetiapine and donepezil has been successful for 22 months.

Both patients responded to donepezil, but its effect on visual hallucinations was attenuated over several months. It seems unclear whether this attenuation was due to the exacerbation of DLB or to the pharmacologic properties of donepezil. Whatever the cause, visual hallucinations gradually became refractory to donepezil, and the addition of 100 to 150 mg/day of quetiapine was effective in reducing hallucinations without serious side effects. Although both cases responded to quetiapine augmentation, quetiapine addition appeared to be more effective for Ms. A than for Mr. B, probably because he was also receiving levodopa.

In conclusion, our case findings suggest that quetiapine augmentation may be effective for donepezil-refractory visual hallucinations in some patients with DLB. Further large open-label studies and randomized controlled trials are required to confirm this effect.

The authors report no financial affiliation or other relationship relevant to the subject matter of this letter.

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Takeshi Terao, M.D., Ph.D.
Taito Shimomura, M.D.
Yukiyo Izumi, M.D.
Jun Nakamura, M.D., Ph.D.
University of Occupational and Environmental Health
School of Medicine
Kitakyushu, Japan