

Talking About the Internet

Sir: The article "Googling Suicide: Surfing for Suicide Information on the Internet" by Recupero et al.¹ demonstrates that while most suicide-related Internet "hits" are either suicide-neutral or anti-suicide, the Internet allows individuals to easily access not only Web sites that furnish detailed instructions on maximizing self-harm but also sites that provide forums for encouragement and support in furtherance of such acts. These findings lead the authors to conclude that "mental health professionals should ask patients about their Internet use."^{1(p878)}

I would agree that clinicians should talk to patients about their lives. They should speak to patients about their relationships, their interests, even their leisure time activities. In short, they should get to know their patients. The last thing contemporary clinicians need, however, is another item added to the "what should be asked about" list—in this case, patients' Internet usage patterns.

Laundry list approaches in both assessment and treatment settings do not result in the establishment of an optimal therapeutic relationship between clinician and patient and at times may even serve to further alienate patients. (This alienation may in fact be what many patients searching the Internet are already feeling.) The best approach remains getting to know your patients—which requires not only asking patients questions but taking the time to listen to their answers.

Dr. Neimark reports no financial or other relationship relevant to the subject of this letter.

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Dr. Recupero and Colleagues Reply

Sir: We agree with Dr. Neimark that psychiatrists must get to know their patients and that doing so requires active listening, not formal checklists. While we by no means recommend a "laundry list" approach to learning about patients' Internet use, we hope that the social history being taken by the clinician will be current with the times.

The presence of pro-suicide Web sites is not the only reason clinicians should be interested in what their patients are doing online. In our interviews with patients, we spoke with manic patients who were using the Internet to locate sex partners, substance-abusing patients who were using online pharmacies to purchase drugs they had not disclosed to their physicians, patients who were harassed online because of their mental illness, and, importantly, many patients who found enormous support and comfort from online support groups and helpful informational Web sites.

The purpose of our article was not to advocate a lengthier "laundry list" approach to clinical interviews, but to underscore

the importance of the Internet in the lives of many patients and to encourage clinicians to help steer vulnerable patients toward more helpful resources on the Web. We agree with Dr. Neimark about the importance of open communication between patients and providers.

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

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Lithium and Suicidal Behavior in Patients With Bipolar Disorder

Sir: We read with great interest the excellent article by Marangell et al.¹ In this case-control analysis of the impact of lithium (and other) pharmacotherapy on prospectively observed suicidal behavior in patients with bipolar disorders, the authors did not find an association between lithium (and other mood stabilizer) use and suicide attempts or completed suicides. This is in contrast with recent meta-analyses^{2,3} showing that in patients with major mood disorders, long-term lithium treatment reduces the risk of suicidal behavior by 60% to 90%. However, in Marangell and colleagues' study, 40 patients out of the 93 suicidal cases (43.0%) and 47 patients out of the 93 nonsuicidal controls (50.5%) were actually on long-term lithium treatment for only 6 months before the last follow-up visit, whereas only 22/93 (23.6%) were on *continuous* long-term lithium treatment in the suicidal cases and 29/93 (31.2%) in the control group. Although these differences are not significant, the lower rates of lithium treatment in suicidal cases than in nonsuicidal controls are in the direction of other studies on lower suicidality in bipolar disorder patients during long-term lithium treatment.^{2,3}

In addition, a recent study⁴ has found that in a Danish population a lower suicide rate was associated with an increased number of prescriptions for lithium salts. In particular, purchasing lithium 2 or more times was associated with a greater decrease in suicide rate compared with purchasing it only once. This finding suggests that including patients with only 1 follow-up visit, as in the study of Marangell et al.,¹ may underestimate the antisuicidal effect of lithium and limit the generalizability of their negative results.

Despite the sophisticated design used in Marangell and colleagues' study, including the information on medication prescription at the last follow-up visit, the authors could not control for the medication status at the time of suicidal event, which occurred within 30 days after the last follow-up visit in all cases. Bipolar patients who are noncompliant with or nonresponsive to lithium have a higher risk of relapse or recurrence *even within the first 4 weeks*⁵ and are more frequently suicidal than their compliant and lithium-responsive counterparts.^{3,4,6} Conversely, patients adhering to treatments and showing good response to them have a greater chance of remaining well and becoming nonsuicidal.^{3,4,6} Therefore, it is possible that noncompliant and lithium-nonresponsive patients were overrepresented among the suicidal cases in Marangell and colleagues' study.¹

As bipolar patients quite frequently stop their medication by their own decision,^{6,7} and symptomatic relapses or recurrence even a few weeks after stopping lithium are not rare,⁸ it would be interesting to clarify the following:

1. how many suicidal cases and controls purchased their last lithium prescription before the suicidal event (or, for controls, the end of the random 6-month period),
2. how many suicidal cases and controls took their lithium continuously until the time of the suicidal event (or, for controls, the end of the random 6-month period), and
3. how many suicidal cases and controls had only 1 post-baseline visit.

Moreover, antidepressants can worsen the long-term course of bipolar disorders,⁹ and concomitant use of antidepressant and antipsychotic medication significantly increases the risk of suicidal behavior in bipolar patients on long-term mood-stabilizing treatment.¹⁰ In addition to the "confounding by indication,"^{1(p921)} as discussed by Marangell et al., the effect of antidepressants can serve as an additional explanation for the finding, i.e., why the association between selective serotonin reuptake inhibitor use and suicidal behavior remained significant, but was less robust, when mood state at the visit prior to the suicide event was included in the matching process. Considering all of the above, it would be interesting to clarify

4. how many patients were on lithium monotherapy during the follow-up (or, at least, at the last follow-up visit) among both the suicidal cases and nonsuicidal controls.

We hypothesize that the negative results from Marangell et al.¹ on the antisuicidal effect of lithium in bipolar patients are the consequence of the higher rate of noncompliant patients and lithium nonresponders among the suicidal cases compared to their nonsuicidal counterparts. This assumption is also supported by the finding from a prior study,¹¹ based on a similar design, showing a nonsignificant difference in the suicidality of lithium-treated patients compared to their matched controls. In that study, the rate of lithium-treated patients was also lower among suicidal cases than in nonsuicidal controls, and the number of depressive symptoms in the week preceding a suicide event was much higher among suicidal than nonsuicidal patients. This difference between the 41 suicide attempters and their controls was highly significant. In addition, Tondo et al.¹² found that 49% of the 252 nonsuicidal and 100% of the 58 suicidal bipolar I or II patients experienced severe depression during long-term lithium treatment, suggesting that suicidal behavior during lithium maintenance is mainly the consequence of treatment nonresponse.

Dr. Marangell was shown this letter but did not comment within the allotted time.

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Extreme Creatine Phosphokinase Elevation in a 20-Year-Old Man Participating in a Clinical Trial of Major Depressive Disorder

Sir: Creatine phosphokinase (CPK) is an enzyme primarily found in cardiac and skeletal muscle as well as in brain tissue and the gastrointestinal tract.¹ More specifically, CPK is involved in the conversion of adenosine triphosphate and creatine to adenosine diphosphate and creatine phosphate via the transfer of a high-energy phosphate.² Minor elevations of CPK occur routinely with strenuous exercise, hypothyroidism, and statin-associated myopathy.^{3,4} Dramatic elevations of CPK (> 10,000 U/L) are more rare and can portend the onset of neuroleptic malignant syndrome or rhabdomyolysis, which in turn could lead to severe complications such as renal damage, kidney failure, and even death.^{5,6} In the following report, we present a case of a young adult man with an extreme CPK elevation noted during a routine clinical trial visit.

Case report. Mr. A is a 20-year-old white man with a history of recurrent depressive episodes, participating in an up to 52-week relapse prevention study of the novel antidepressant agomelatine. He had no history of alcohol or drug abuse

or heart, muscle, or liver disease. Assigned to open-label agomelatine, Mr. A had a brisk antidepressant response by week 8. After 20 weeks on agomelatine treatment, he was randomly assigned to either agomelatine or placebo.

Eleven weeks after randomization, in March 2008, the patient reported a 1- to 2-week worsening of depressive symptoms and met criteria for relapse, and an early termination visit was performed as per protocol. The patient, while somewhat more depressed, was physically asymptomatic at the early termination visit, but reported taking 2 "Centrum Performance" multi-vitamins daily for 1 week and that he had begun a workout regimen. He proudly reported that he had purchased a piece of fitness equipment, with accompanying DVD, called "Perfect Pushup" and was strictly following this program.

The laboratory results from this visit came back 3 days later and showed an extremely elevated CPK level of 10,580 U/L (reference: 35–232 U/L) as well as an elevated aspartate aminotransferase (AST) level of 179 U/L (reference: 0–42 U/L) and an elevated lactate dehydrogenase (LDH) level of 436 U/L (reference: 100–242 U/L). Alanine aminotransferase (ALT) and bilirubin levels were within normal limits. Mr. A was contacted immediately, and he denied any symptoms except some mild "soreness" from the workouts. He had no significant muscle pain and no change in urine color or other symptoms. Physical examination and electrocardiogram results were normal. The patient was told to stop all workouts and refrain from taking any vitamins or supplements, although he admitted to another strenuous workout 2 days earlier.

The next day, the patient returned to the clinic, and repeat chemistry tests were run. He continued to be asymptomatic. Laboratory results showed a CPK level of 13,950 U/L, an AST level of 407 U/L, and an LDH level of 276 U/L. The patient's ALT level was now elevated at 176 U/L (reference: 0–48 U/L). His CPK-MB isoenzyme, bilirubin, blood urea nitrogen, and serum creatinine levels were within normal limits. Urine myoglobin, hepatitis B surface antigen, and hepatitis C antibody test results were negative. After the receipt of these results, a serious adverse event report was filed with the study sponsor, and the patient was scheduled for an Internal Medicine consultation. Upon questioning, the patient admitted to taking 1 to 2 scoops of a "protein supplement" (with creatine listed as a main ingredient) on 2 separate occasions. On each occasion, Mr. A took the product 2 days prior to blood collection. He also admitted that his workouts were intense, with at least 8 heavy workouts with weights and pushups in the 10 to 14 days prior to the first blood draw. He denied using anabolic steroids or other performance enhancing drugs. A urine drug screen was negative.

Seven days after the early termination visit, a third set of laboratory examinations was performed. These results showed a CPK level of 1628 U/L. The patient's AST and ALT levels had decreased to 101 U/L and 103 U/L, respectively.

Mr. A came in for a final visit a week and a half later. He continued to be asymptomatic and had refrained completely from exercise since the last visit. Laboratory results showed normal CPK, AST, and ALT levels (105, 16, and 19 U/L, respectively; Table 1).

While at first the study medication was suspected as a possible contributor to the extreme CPK elevation, upon further investigation, other explanations became more plausible. The patient had no CPK elevation during the 20 weeks he was taking agomelatine prior to the early termination visit (levels were checked at weeks 2, 4, 8, 16, and 20), making a relationship to study medication very unlikely. The creatine supplement was also suspected, but a literature search revealed this too to be an unlikely cause of such an extreme elevation.⁷ Multiple sets of

Table 1. Laboratory Results for a 20-Year-Old Man Participating in a Clinical Trial of Major Depressive Disorder^a

Timepoint	CPK (35–232)	ALT (0–48)	AST (0–42)	LDH (100–242)
Screening	182	14	22	145
Open-label week 2	132	13	18	138
Open-label week 4	196	14	18	145
Open-label week 8	110	10	18	139
Open-label week 16	85	13	17	117
Open-label week 20	106	16	18	135
Double-blind week 1	86	12	19	144
Double-blind week 8	88	12	19	129
Early termination	10580	47	179	436
Day 4 after early termination	13950	176	407	276
Day 7 after early termination	1628	103	101	145
Day 18 after early termination	105	19	16	114

^aValues are expressed as U/L. Reference ranges are shown in parentheses. Values > 3 times the upper limit of normal are shown in boldface type.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, CPK = creatine phosphokinase, LDH = lactate dehydrogenase.

intense arm muscle exercise, similar to what the patient described with his "Perfect Pushup" regimen, have been shown to lead to extreme CPK elevations. In one study, 51 of 203 subjects engaged in an eccentric exercise regimen showed CPK elevations greater than 10,000 U/L.⁸ In another report, a police recruit had a CPK of 87,335 U/L and rhabdomyolysis caused by repetitive intense exercise.⁹

In long-term clinical trials such as this relapse-prevention study of major depressive disorder, patient-specific behaviors are more likely to show up as confounding variables in laboratory safety testing. Subjects should be cautioned not to change their routines—medications, supplements, therapies, and other lifestyle behaviors—during the course of clinical trials, some of which may last a year or longer. Careful and repeated exploration of lifestyle factors is necessary before an investigator can determine the role of study medications in clinically significant laboratory abnormalities.

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Suicidal Ideation and Varenicline: A Possible Case of Mistaken Adverse Drug Reaction?

Sir: Varenicline, an $\alpha_4\beta_2$ nicotinic acetylcholine partial agonist, has been licensed in the United Kingdom (and approved in the United States) for the treatment of tobacco dependence since 2006.^{1,2} Studies have shown varenicline to result in higher smoking cessation rates over placebo, bupropion, and nicotine replacement therapy (NRT).³⁻⁵ In the one study⁴ conducted to date, varenicline was also seen to be effective in smokers with mental illness, there being no evidence of excess adverse events or exacerbation of preexisting conditions. Craving to smoke is the symptom most predictive of relapse in the period immediately following a cessation attempt.⁶⁻⁸ Varenicline appears to achieve improved efficacy by more effectively reducing craving than other therapies, while being similarly effective in reducing other tobacco withdrawal symptoms, such as depression, irritability, and poor concentration.³⁻⁵

Notwithstanding the impressive results achieved with varenicline, there has been sufficient concern over reports of depression and suicidal ideation with varenicline to prompt drug safety updates from the Medicines and Healthcare Products Regulatory Agency⁹ and the U.S. Food and Drug Administration.¹⁰

However, such concerns need to be seen in the context of the established association between smoking and both mood disorders and suicidal behavior.¹¹⁻¹⁴ It can therefore be expected that the postmarketing surveillance of new smoking treatments will identify a disproportionate number of cases of depression and suicidal ideation, regardless of any potential for adverse drug reactions. A recent case of suicidal ideation in a smoker prescribed varenicline at our clinic (1 out of approximately 500 cases in whom varenicline was used) has suggested the additional possibility that a higher incidence of severe depression as a result of tobacco withdrawal might be expected with treatments, such as varenicline, that suppress craving more effectively over a longer period.

Case report. Despite his repeated quit attempts over many years, including earlier treatment at our clinic using NRT, Mr. A, aged 40 years, had not managed to abstain from smoking for more than 2 or 3 days. At baseline assessment for the NRT treatment episode, a history of depression was noted. Throughout treatment, the self-completed Maudsley Tobacco Withdrawal Symptoms Scale was used to assess changes in mood and desire to smoke.⁴ During Mr. A's first week of trying to stop smoking,

ratings of craving increased to "moderate," with some strong urges to smoke, while depressive symptomatology also increased from "slight" to "moderate." Only 2 days of abstinence were achieved, and normal smoking was resumed the following week.

At baseline assessment in January 2008 for the recent treatment with varenicline, "slight depression" was again reported. These and other mood symptoms remained stable throughout a week of complete abstinence from smoking. Varenicline (1 mg twice daily) was described as "very helpful" during this time by the patient, who reported only a "slight" craving to smoke. However, during the second week of abstinence, his mood deteriorated progressively to culminate in ratings of "severe/extreme" depression and transient suicidal ideation at the end of the week. Varenicline had not been taken since the previous evening, and none was taken subsequently. Smoking was resumed that day, and mood gradually improved.

One week later, tobacco consumption and depression ratings had returned to baseline levels. At follow-up 2 and 6 weeks later, Mr. A's mood remained stable. On the latter occasion, he commented that although he had originally thought that varenicline had caused the suicidal ideation, on reflection he believed it could have been a result of stopping smoking.

This event is compatible with either an adverse drug reaction or severe tobacco withdrawal symptoms. Considering the latter possibility, it might be relevant that the earlier treatment episode showed a susceptibility to postabstinence depression, although on that occasion smoking was resumed after only 2 or 3 days, before possible further mood deterioration. With varenicline, 12 days of abstinence was achieved, and it was only during the last days that mood deteriorated significantly. It may be hypothesized that because varenicline suppressed craving to smoke for longer, it also gave time for more severe mood disturbance to emerge. Although the alternative explanation of an adverse drug reaction remains possible, it is not well supported by the fact that varenicline had already been taken for more than 2 weeks before any deterioration in mood.

This case, and the possible interpretation of severe tobacco withdrawal symptoms rather than an adverse drug reaction, has wider relevance. It might be appropriate for current clinical guidelines for smoking cessation treatment to be revised, advising all clinicians treating smokers to routinely monitor mood, especially in those with a history of mood disorder, regardless of the treatment given.

Mr. Stapleton and Ms. Sutherland have either acted as advisers to the manufacturers of NRT and varenicline or given lectures on tobacco dependence sponsored by the manufacturers of NRT and varenicline, for which they have received remuneration. Dr. Spirling reports no financial or other relationship relevant to the subject of this letter.

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