

## NEUROBIOLOGY OF SUICIDE

J. John Mann, M.D.

Required reading: Mann JJ. "The Neurobiology of Suicide." Nature Medicine 4:25-30. 1998.

Epidemiology of suicide in the U.S.:

- ninth leading cause of death
- over 30,000 suicides every year
- about 300,000 suicide attempts every year

Suicidal behavior occurs most commonly in patients with mood disorders. Alcohol and substance abuse, schizophrenia, and personality disorders are also associated with an increased risk of suicide.

Risk factors: Patients with a low threshold for suicidal behavior who experience a trigger are at high risk for making a suicide attempt.

1) Threshold: Degree of impulsivity can be thought of as a trait that does not vary much over time in a particular individual.

- Evidence from study of 100 depressed patients followed over 12 years: Those who attempted suicide had higher levels of lifetime impulsivity than those who did not.

- Patients with higher lifetime impulsivity are more likely to have a family history of suicidal behavior, suggesting that this trait may be inherited. An adoption study found a six-fold increase in completed suicide in the biological families of adoptees with a history of suicide, as compared with adoptees with no history of suicide. This association persists even when presence of psychiatric illness in families is controlled for.

2) Trigger: A trigger can be thought of as state-dependent. Common triggers for suicidal behavior include major depressive episodes and stressful life events.

## 1) NEUROCHEMICAL ABNORMALITIES:

- CSF 5-HIAA is lower in depressed patients with a history of lethal suicide attempts. The more lethal the attempt, the lower the 5-HIAA. This finding is not related to when the attempt occurred (i.e. the abnormality persists and seems to reflect a low threshold in these patients).

- Low CSF 5-HIAA is also associated with more lifetime impulsive aggression (in non-human primates as well as in people).

- PET studies indicate abnormal metabolism in the prefrontal cortex of impulsive murderers.

## 2) RECEPTOR ABNORMALITIES:

- Post-mortem receptor-binding studies indicate abnormalities in the ventral prefrontal cortex of patients who committed suicide:

- reduced serotonin transporter site binding indicative of reduced serotonin input

- increased serotonin post-synaptic receptor binding

Both of these receptor-binding findings are consistent with decreased serotonin, since the post-synaptic receptor increase could be a compensatory up-regulatory mechanism. The prefrontal cortex seems to play a role in mediating inhibition.

3) GENE MARKER: The less common "UU" genotype for the tryptophan hydroxylase enzyme, responsible for the synthesis of serotonin, occurs more frequently in suicide attempters with major depression than the "LL" form.

4) CELL ALTERATIONS: Post-mortem study of suicide victims found that serotonin neurons are increased but are smaller and oddly-shaped, suggesting a developmental defect.

## The neurobiology of suicide

Suicide accounts for over 30,000 deaths in the United States annually<sup>1</sup>, and is almost always a complication of a psychiatric illness.

Lifetime mortality due to suicide is approximately 15% in individuals suffering from recurrent depressive episodes, 20% in bipolar patients, 18% in alcoholics, 10% in schizophrenia, and 5–10% in certain types of personality disorders<sup>2-3</sup>. Despite dramatic improvements in the medication treatment of psychiatric disorders, there has been relatively little change in suicide rates over the last quarter of a century. Reasons for the apparent failure of improved medication treatment to reduce suicide rates have been identified. Common myths regarding causal factors in suicide will be addressed. The development of a more complete model of suicidal behavior that takes into account a large body of recent findings regarding neurobiological correlates of suicide risk will be described.

### Definition of suicidal behavior

Suicidal behavior spans a spectrum that ranges from completed suicide to suicide attempts and, at the mildest end, suicidal ideation. This review will focus on suicide attempts defined as a self-damaging act carried out with at least some intent to end one's life, and will not include various other forms of apparently self-destructive behavior such as self mutilation, failure to cooperate with medical treatment in severely ill patients, cigarette smoking and alcohol abuse. Suicide attempts are more complex than completed suicide since they include a medical damage dimension, ranging from individuals who survive a very serious suicide attempt by good fortune to individuals who sustain little or no injury, and a second axis which may be partially orthogonal to the first, and involves suicidal intent<sup>4</sup>. Taking into account these aspects of suicidal behavior, it is possible to generate broad categories that nevertheless overlap. The first category is that of failed suicide<sup>5</sup>, where a highly lethal method is used that inflicts considerable medical damage and is accompanied by careful preparation and planning. At the other end of the attempt spectrum is a suicide attempt that involves a low lethality method, inflicts little medical damage and the level of objective intent or planning is relatively low. This latter category has been termed pseudocide or suicide gesture<sup>6</sup>. It generally occurs spontaneously in a setting of an acute conflict in a close relationship. This review will focus mainly on more lethal suicide attempts involving serious intent to die, as well as completed suicide.

### Clinical correlates of suicidal behavior

Suicide is almost always a complication of a psychiatric illness. Over 90% of cases have a significant psychiatric illness<sup>8-12</sup>. The most common illness reported is a mood disorder that generally accounts for 60% of cases, with major depression being the most common. The remaining cases are associated with schizophrenia, alcoholism, substance abuse, personality disorders, Huntington's disease and epilepsy. Thus, suicide is not merely a complication of a personal crisis or a psychosocial setback, but occurs in the context of a psychiatric illness. Patients with major depression sometimes describe an emotional pain that feels worse than any physical pain they have ever experienced.

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Given that many depressed patients also feel hopeless about recovery, in such a case, suicide may be understood as an effort to seek relief from this emotional pain. However, most patients with a psychiatric illness do not commit suicide. We have previously reported that individuals who make medically serious suicide attempts in the context of a recurrent depressive illness, do so relatively early in the illness<sup>13</sup>. Moreover, suicide attempters tend to make multiple attempts with increasing lethality over the same period of risk as individuals with the same level of severity of major depression who never make a suicide attempt. This suggests some patients have a vulnerability or predisposition to suicidal behavior. Suicide is not simply a logical response to extreme stress. On the basis of these observations, we have proposed a stress diathesis model of suicidal behavior (Fig. 1). Typical stressors (Fig. 1a) associated with suicidal acts include: the psychiatric illness; acute use of alcohol or sedatives that appear to disinhibit patients; an acute medical illness, especially if it affects the brain; and adverse life events.

Most of the recent advances in understanding risk factors in suicidal behavior have come from a recognition that the diathesis or predisposition to suicidal behavior is a key element that differentiates psychiatric patients who are at high risk versus those at lower risk. The objective severity of the psychiatric illness does not assist greatly in distinguishing patients at risk for suicide attempts or suicide compared to those who are not at risk. Variations in the diathesis may explain why one person commits suicide during a depressive episode and another does not. Thus, suicide attempters appear to react differently to the

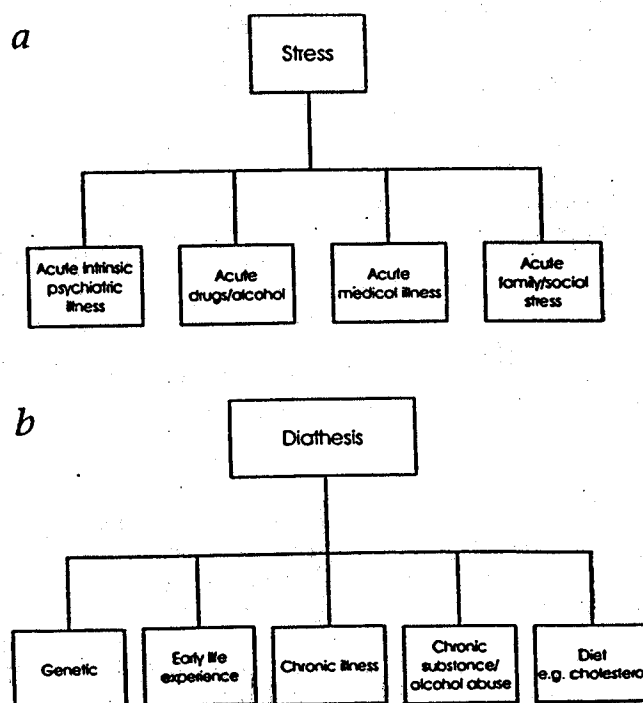


Fig. 1 A stress-diathesis model of suicidal behavior: Components of stress and diathesis.

same objectively determined level of severity of depression. Understanding why the diathesis or vulnerability to suicide differs across patients can assist in improved screening of high-risk patients and treatment. As illustrated in Fig. 1b, the diathesis for suicidal behavior is influenced by genetic factors<sup>14-16</sup>; rearing<sup>17</sup>; chronic illness, especially affecting the brain such as epilepsy<sup>18</sup>; migraine<sup>19</sup> and Huntington's disease<sup>20,21</sup>; alcoholism and substance abuse<sup>4,10,22-24</sup>; and cholesterol level<sup>29,30</sup>.

Many investigators have focused on specific symptom components of the acute psychiatric illness<sup>31</sup>, such as the presence of delusions in people with major depression<sup>32</sup>, comorbid panic attacks or anxiety symptoms<sup>33</sup>, mixed mood states in patients with bipolar disorder or manic depression where features of both mania and depression are intermixed and, in schizophrenia, the presence of paranoid delusions together with less pronounced deficit symptoms such as apathy, cognitive deficits and inaction<sup>34</sup>. Although these studies are of theoretical interest, they have done little to help improve clinical detection of high risk patients because the increased risk associated with any of these specific clinical characteristics is too small to be useful in the clinical care of an individual case.

#### Neurobiological correlates of completed and attempted suicide

A large number of studies in postmortem brain tissue from suicide victims have been carried out examining indices of the serotonergic, noradrenergic and dopaminergic neurotransmitter systems (for review, see ref. 35). Studies of the serotonergic system have generally found decreases in presynaptic serotonin nerve terminal binding sites such as the serotonin transporter site and a related serotonin nontransporter nerve terminal binding site<sup>36</sup>. More recent autoradiographic studies of post-mortem brain tissue have suggested that these abnormalities are more pronounced in the ventral prefrontal cortex than in the dorsolateral prefrontal cortex<sup>37</sup>.

Similarly, postsynaptic serotonin receptors, such as the 5-HT<sub>1A</sub> receptor and the 5-HT<sub>2A</sub> receptor, appear to be increased in number in the prefrontal cortex of suicide victims. The explanation for the increases in these subtypes of postsynaptic serotonin receptors is uncertain, but one possibility is compensatory upregulation in response to reduced serotonin neuron activity. These receptor changes appear to be more pronounced in the ventral prefrontal cortex<sup>37</sup>. A convergence of altered serotonin receptor binding indices in the ventral prefrontal cortex would indicate that this brain region is of particular importance in relation to the risk for suicide. The reduction in the presynaptic, serotonin nerve terminal transporter binding, and the increase (possibly compensatory) in postsynaptic 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptor binding is consistent with the notion that serotonin input into this brain region is reduced.

The ventral prefrontal cortex is involved in the executive function of inhibition<sup>38</sup> and injuries to that area of the brain can result in disinhibition<sup>39</sup>. Reduced serotonergic input into this part of the brain may result in impaired inhibition and a greater propensity to act on powerful feelings such as suicidal or aggressive feelings. Lifetime externally directed aggression is more frequent in suicide attempters and *vice versa*. Both behaviors are associated with reduced serotonergic function (for review, see ref. 40). Aggression is also associated with ventral prefrontal lesions; this area of the brain may mediate a more universal restraint mechanism that is suboptimal in some suicidal patients, as well as in association with aggression (Fig. 3).

In support of the above hypotheses, most studies of brain-

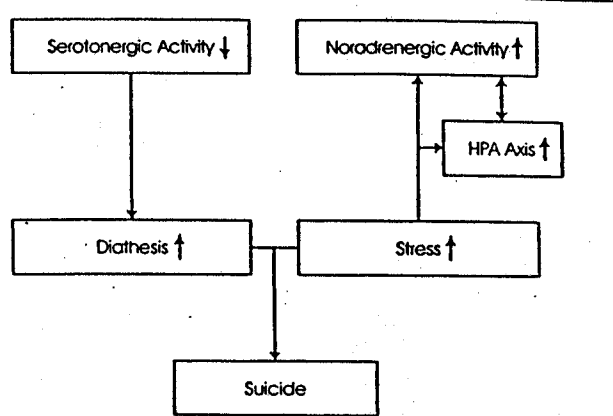


Fig. 2 Neurobiology of completed suicide

stem levels of serotonin or its major metabolite, 5-hydroxyindole acetic acid (5-HIAA), have found modest reductions<sup>41</sup>. This would suggest that serotonergic activity may be reduced in suicide victims. The brainstem results are consistent with receptor findings and with reports of reduced levels of cerebrospinal fluid 5-HIAA in individuals with a history of serious suicide attempts<sup>42</sup>.

A number of alterations in noradrenergic indices are also reported in suicide victims, although the results are less consistent than those for the serotonergic system<sup>35</sup>. There is evidence that the number of noradrenergic neurons in the locus coeruleus is reduced in suicide victims<sup>43</sup>. Fewer noradrenergic neurons could be due to developmental cause, and are less likely to be due to nonspecific illness or stress effects. In addition, levels of norepinephrine appear to be lower in the brainstem of suicide victims and  $\alpha_2$ -adrenergic autoreceptor number is increased<sup>44</sup>. Levels of tyrosine hydroxylase, the rate-limiting enzyme in the biosynthesis of norepinephrine, are increased<sup>45</sup>. Tyrosine hydroxylase activity increases under circumstances of increased norepinephrine release and depletion as a compensatory mechanism.  $\alpha_2$ -adrenergic autoreceptor upregulation can also occur when norepinephrine is depleted. These results suggest noradrenergic depletion. In the prefrontal cortex, although  $\beta$ -adrenergic binding is generally reported to be high, we have found that the high affinity component of  $\beta_1$ -adrenergic binding is actually decreased (Arango, Underwood & Mann, unpublished data), suggesting there may also be a shift to the low affinity conformational state in  $\beta_1$ -adrenergic receptors. To account for the reports of an overall increase in  $\beta$ -adrenergic binding, one would have to postulate that  $\beta_2$ -adrenergic binding is increased. We have also reported that norepinephrine levels in the prefrontal cortex are increased and that  $\alpha$ -adrenergic binding is decreased<sup>46</sup>. This combination of observations suggests that there has been noradrenergic overactivity. Such overactivity may have resulted in depletion of norepinephrine from the smaller population of noradrenergic neurons found in suicide victims. Studies of chronic stress in rodents report depletion of norepinephrine. There is evidence of hyperactive stress response systems reported in depression<sup>47,48</sup>. Thus, these biochemical findings could potentially be a result of the stress preceding a suicidal event in a serious psychiatric illness.

Few studies have been carried out on the dopaminergic system. Decreased D<sub>1</sub> and D<sub>2</sub> dopaminergic binding in the prefrontal cortex of adolescent suicide victims has been reported,

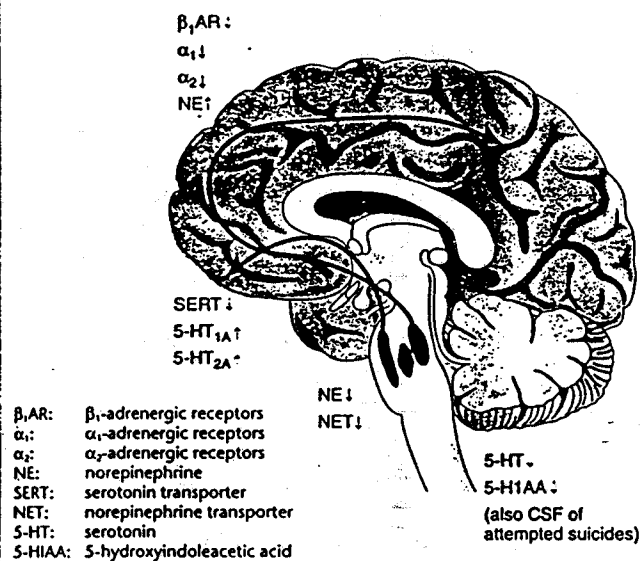


Fig. 3 Neurobiology of suicide at the circuitry level

but studies are too few to confidently determine whether there are changes in dopamine or homovanillic acid (HVA), its major metabolite, in either prefrontal cortex or brainstem. Given the reports of reductions in CSF HVA in suicide attempters subject to major depression<sup>49</sup>, and reports linking reduced dopaminergic function to major depression<sup>50</sup>, it would be of great interest to further evaluate the dopaminergic system in suicidal patients. Studies of other neurotransmitter systems are still too preliminary to discuss.

The serotonergic correlations with suicide appear to be equally strong regardless of the associated psychiatric disorder. Therefore, the serotonergic abnormality in the brain of suicide victims may be related to the predisposition to suicidal behavior, rather than to the psychiatric illness that may have triggered it.

The serotonergic changes are more likely to be related to the vulnerability or diathesis for suicidal behavior based on the observations that the level of serotonergic system activity shows considerable stability over time, and is under substantial genetic control<sup>51</sup>. Demonstrating the interaction of genetics and environment, peer-reared monkeys when compared to maternally raised monkeys have their serotonergic activity reset to a lower level that persists into adulthood. The rank order of their serotonergic activity is not altered within the peer-raised monkeys; each monkey's activity is lowered by a comparable proportion. Thus, the effects of rearing are superimposed on the genetic effects. Given that a history of child abuse is associated with a greater risk for suicidal behavior in adult life, extrapolating from the monkey studies, it is possible that child abuse resets serotonergic function at a lower level and this neurochemical effect persists into adulthood, contributing to the increased risk for suicidal behavior. Therefore, the serotonergic system fulfills the criteria for a biochemical trait. In contrast, the noradrenergic system is more state dependent, under less genetic control<sup>51</sup> and, perhaps, reflects responses due to the acute stress of the psychiatric illness or in relation to the suicidal act (see Fig. 2). The stress of feeling desperate and suicidal may result in excessive noradrenergic activity and consequent depletion in that stress-response neurotransmitter system.

With regard to that possibility, studies of the stress systems, including the hypothalamic pituitary adrenal axis (HPA), are of great interest because corticotrophin releasing hormone and corticosteroids can modulate both noradrenergic and serotonergic activity. Major depression is often associated with hyperactivity of the HPA axis<sup>52</sup>, and suicidal patients may exhibit even greater hyperactivity<sup>53,54</sup>. Thus, there is evidence from studies of both the HPA axis and brain noradrenergic indices consistent with the presence of chronic stress responses that may contribute to the risk for suicide. If this hypothesis can be confirmed, relief of stress effects may help to enhance therapeutic interventions.

Two thirds of major depressives that have attempted suicide were found to have lower CSF 5-HIAA levels compared to non-attempters with the same psychiatric diagnosis. Consistent with the notion of a biochemical trait<sup>51</sup>, low CSF 5-HIAA predicts future suicide attempts and suicide completion<sup>55-56</sup>. Similarly, lower CSF 5-HIAA has been found in schizophrenics with a history of suicidal behavior compared to schizophrenics without such a history, and also in individuals with personality disorders who make suicide attempts compared to patients with the same diagnosis who do not. Low CSF 5-HIAA, therefore, appears to be a relatively stable marker that is associated with suicide attempt behavior in a number of psychiatric disorders, analogous to the association between low brainstem levels of serotonin or 5-HIAA in suicide victims, independent of psychiatric diagnosis.

Individuals with major depression or personality disorders that have attempted suicide have a blunted prolactin response elicited by the serotonin releasing drug, fenfluramine. The more lethal the suicide attempt, the more likely there is to be low CSF 5-HIAA or a blunted prolactin response to fenfluramine<sup>59,61</sup>.

Serotonin mediates a number of platelet functions, some of which are altered in suicide attempters. Upregulation of 5-HT<sub>2A</sub> receptors on the platelets of suicide attempters correlates with the severity of the most recent suicide attempt<sup>62</sup>.

Thus, three different indices of serotonergic function appear to correlate with suicidal behavior in patients independent of diagnosis, namely CSF 5-HIAA, the prolactin response to fenfluramine, and platelet 5-HT<sub>2A</sub> receptor binding. Finally, a polymorphism in the gene for tryptophan hydroxylase, the rate-limiting enzyme in the biosynthesis of serotonin, has been shown to be associated with suicidal behavior in impulsive alcoholic criminals<sup>63</sup> as well as in individuals with major depression<sup>64</sup>. If these two studies are correct, there is a link between genetics, serotonergic function and suicidal behavior.

If lower serotonergic activity contributes to suicide risk, then it is of interest to know what factors influence both and perhaps, therefore, affect suicide risk via the serotonergic system. Fig. 4 illustrates several such factors. As indicated above, genetic factors, a deprived upbringing, low cholesterol, and substance abuse can all be associated with or induce lower serotonergic activity. The factors are also associated with greater suicide risk, perhaps because of lower serotonergic activity. Males commit suicide two to three times more often than females and have lower serotonergic activity than females. If confirmed, this hypothetical model suggests that increasing serotonergic activity may be a valuable therapeutic approach that can work in a variety of circumstances to reduce the risk of serious suicidal behavior.

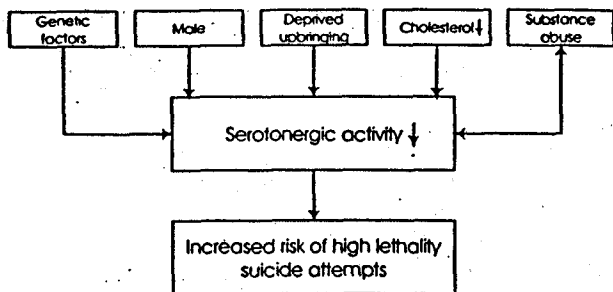


Fig. 4 Neurobiology of attempted suicide

#### Suicide aggression, impulsivity and neurobiology

Individuals with major depression and personality disorders who have a history of suicidal behavior, also have a greater lifetime history of aggression and impulsivity. Criminals who have a history of suicidal behavior, also have a history of more severe aggression than criminals who do not have a history of suicidal behavior<sup>65,66</sup>. Thus, there may be a fundamental predisposition to more impulsive behavior, whether it is self-directed, in the form of suicidal behavior, or externally-directed, in the form of aggression against property or other persons. These observations have acquired new importance recently with reports that impulsive, externally-directed aggression is associated with low CSF 5-HIAA<sup>67,68</sup>. Low CSF 5-HIAA has been shown to be present in impulsive murderers and arsonists compared to non-impulsive murderers and other criminals as well as control subjects<sup>69</sup>. A blunted prolactin response has been reported in association with aggressive behavior and impulsivity in individuals with personality disorders, major depression and medically healthy volunteers<sup>70</sup>. Thus, reduced serotonergic function appears to be associated with impulsive aggression, and has also been reported to predict recidivism in murderers<sup>70</sup>. This relationship is analogous to that between serotonergic function and suicidal behavior and leads to the more general hypothesis that serotonergic function supports a restraint mechanism, and a deficiency of serotonergic function results in greater impulsivity and aggression that also includes self-directed aggression in the form of suicidal behavior.

Studies from nonhuman primates confirm a relationship between aggression, risk-taking behavior and low levels of CSF 5-HIAA<sup>71</sup>. Both these behaviors, as well as serotonergic function, appear to be under genetic control<sup>71</sup>.

Nongenetic factors have also been shown to influence both serotonergic function and behavior. For example, low levels of cholesterol or cholesterol-lowering treatments increase the probability of suicidal behavior and, at least in nonhuman primates, decrease serotonergic function selectively<sup>72</sup>. A low cholesterol diet in nonhuman primates is associated with not only lower serotonergic function, but an increase in aggressive behaviors and a decrease in social contact. Thus, cholesterol levels appear to have a measurable, although small, effect on behavior involving aggression and suicidality. The link between the serotonergic system and cholesterol level remains to be demonstrated in human subjects.

Abuse in childhood has been associated with a higher rate of suicidal behavior in adults<sup>17</sup>. Peer-raised monkeys have lower serotonergic activity than maternally-raised monkeys. In the absence of a model of active abuse, this deprivation model in nonhuman primates suggests that the serotonergic system can

be reset lower, in an enduring fashion, by an impoverished upbringing. By extrapolation, one may hypothesize that active abuse may also reduce serotonergic activity in an enduring fashion, and reset it at a lower level. Such a change would increase long-term risk for suicidal behavior. Direct studies of this hypothesis in human subjects are awaited.

#### Failure of psychotropic medication to impact suicide

Over the last 35 years, there have been immense advances in the development of effective medications for the treatment of mood disorders, schizophrenia, panic disorder and other psychiatric conditions. Disappointingly, there has been little reduction in suicide rates. The results of psychological autopsy studies in several countries suggest the reason. If one examines individuals who have committed suicide in the context of major depression, most studies find that 10–14% of these individuals have received adequate doses of antidepressant treatment<sup>73</sup>. This is not due to a failure to contact health care professionals, as most studies report that the majority of patients, between 50% and 80%, have seen a health care professional within 30–90 days of suicide. Thus, it appears that there is the potential for more effective recognition of psychiatric conditions such as major depression, and the treatment of these conditions with adequate doses of antidepressants in terms of reducing suicide rates. A study carried out in Götland, Sweden involving education of primary care physicians in the diagnosis and treatment of depression, produced an increase in prescription rates of antidepressants and a decrease in suicide rates<sup>74</sup>. Similar results have been reported elsewhere. The Swedish experience suggests that this benefit lasts for a couple of years and then fades. Thus, education at regular intervals has the potential for benefit in the diagnosis and treatment of depression.

Choosing the best medication depends partly on the psychiatric disorder associated with suicidal ideation. Some studies suggest that selective serotonin reuptake inhibitors (SSRIs) produce a more rapid amelioration of suicidal symptoms in patients with major depression<sup>75</sup>. This observation is consistent with a model of suicidal behavior that posits reduced serotonergic activity as underlying the vulnerability to suicidal behavior in the presence of major depression, or any other psychiatric disorder that is accompanied by suicidal ideation. Clozapine, an atypical antipsychotic medication, has been reported to be associated with less suicidal behavior in schizophrenia than typical antipsychotics. Clozapine is atypical in sparing striatal D<sub>2</sub> dopamine receptors that are blocked by typical antipsychotics, resulting in extrapyramidal symptoms. It also has a higher affinity for blockade of 5-HT<sub>2A</sub> receptors. Which of these properties gives it an advantage in suicidal schizophrenics remains to be determined. We are yet to determine the potential of SSRIs in ameliorating suicidal risk in patients with schizophrenia, alcoholism and personality disorders. Lithium, which enhances serotonergic activity, appears to reduce suicide risk in bipolar patients, providing further support for a role of serotonin in moderating suicide risk.

Treating patients with newer antidepressants, such as the selective serotonin reuptake inhibitors, instead of older antidepressants, such as the tricyclics that are more lethal on overdose, has the potential for reducing suicide rates<sup>75</sup>. Non-antidepressant sedative medications, such as barbiturates or benzodiazepines, should be avoided in the treatment of patients with mood disorders. Failure to improve the mood disorder, com-

bined with potential disinhibition by these sedatives and their lethality on overdose, makes for a risky treatment strategy.

Another area of potential prevention is restriction of access to very lethal substances, such as pesticides, which account for an extremely high suicide rate in rural China and Sri Lanka. Gun control has also been proposed as a method for reducing suicide risk<sup>76</sup>. More lethal methods reduce the chance of surviving a suicide attempt.

#### Future Directions

A fundamental challenge is how to improve recognition of psychiatric patients at greater risk for suicide. It is hoped that refocusing of clinical attention on characteristics that reflect a diathesis or predisposition for suicidal behavior will lead to better detection of high-risk patients. Such factors include a past history of suicidal behavior, a family history of suicidal behavior, evidence of impulsive aggression throughout life and suicidal ideation or hopelessness disproportionate to the objective severity of depression. Neurobiological measures or testing may ultimately improve the clinician's ability to detect high-risk patients. These measures currently involve measurement of CSF 5-HIAA but, in the future, newer techniques involving functional brain imaging of serotonergic activity and candidate gene markers hold promise. Given the rapid advances in PET and SPECT imaging of serotonergic function *in vivo*, and the identification of polymorphisms in serotonin-related candidate genes, we now have the tools for developing neurobiological tests to detect patients at high risk for suicide. Such tests may facilitate the testing of treatment interventions that may ultimately reduce the rate of suicide from the current level of over 30,000 deaths per year.

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Department of Neuroscience, New York State Psychiatric Institute  
and

Department of Psychiatry, Columbia University  
722 West 168th Street, Box 28  
New York, NY 10032

Correspondence should be addressed to J.J.M.  
email: [jjm@columbia.edu](mailto:jjm@columbia.edu)